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BACTERIOSTATIC PROPERTIES OF SULFANILAMIDE AND SOME OF ITS DERIVATIVES

I. SUCCINYLSULFATHIAZOLE, A NEW CHEMOTHERAPEUTIC AGENT LOCALLY ACTIVE IN THE GASTROINTESTINAL TRACT

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A systematic study to find a satisfactory drug to alter the bacterial flora of the intestinal tract was undertaken after it became apparent that sulfanilylguanidine has a limited application in the surgical treatment of diseases of the gastrointestinal tract. Sulfanilylguanidine, according to the original reports of Marshall, Bratton, White and Litchfield [1] and Firor and Jonas,[2] seemed to offer great possibilities in this field. However, additional experience presented by Firor and Poth [3] showed that this drug is not satisfactory because (1) the drug is too readily absorbed from the gastrointestinal tract, giving rise to frequent and occasionally severe reactions, and (2) is ineffectual in the presence of ulcerating lesions of the bowel.

The present investigation was undertaken to find an active drug which is not absorbed from the gastrointestinal tract in sufficient quantities to cause toxic manifestations and which is effective in the presence of ulcerating lesions of the intestinal mucosa. It soon became apparent that to find a drug which is effective in the lumen of the

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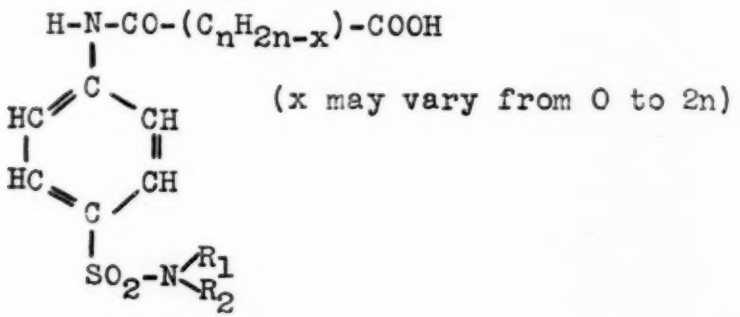
1. Marshall, E. K., Jr.; Bratton, A. C.; White, H. J., and Litchfield, J. T., Jr.: Sulfanilylguanidine: A Chemotherapeutic Agent for Intestinal Infections, Bull. Johns Hopkins Hosp. **67**:163, 1940.

2. Firor, W. M., and Jonas, A. F.: The Use of Sulfanilylguanidine in Surgical Patients, Ann. Surg. **114**:19, 1941.

3. Firor, W. M., and Poth, E. J.: Intestinal Antisepsis with Special Reference to Sulfanilylguanidine, Ann. Surg. **114**:663, 1941.

bowel and is not inhibited by paraaminobenzoic acid [4] and like substances, one must discover a compound which is not active through the free amino group of sulfanilamide and its ordinary derivatives or a compound which will attain a high concentration inside the cell of the bacterium, either because of differential absorption or because the concentration of the drug in the medium can be kept at a high level without toxicity to the host. With such a compound it might be possible by mass action to shift the equilibrium away from the paraaminobenzoic acid effect and get activity in the presence of inhibitors. To this end the study of a series of compounds with free carboxyl radicals was undertaken.

A number of substances were found to possess bacteriostatic activity even when the primary amino group on the benzene ring of sulfanilamide or one of its derivatives had been conjugated with dibasic organic acids to form substituted acid amides. The general formula for this series of amic acids can be represented as follows: [5]



It was observed that the conjugated derivatives were not directly responsible for the local bacteriostatic activity in the gastrointestinal tract. It soon became evident, however, that those compounds which were easily hydrolyzed and consequently resulted in readily absorbed split products gave rise to toxic manifestations, whereas those substances not readily split by mineral acids but requiring sodium hydroxide for saponification were poorly absorbed from the bowel and did not possess toxic properties, although they did have bacteriostatic activity, as was indicated by their effect on the coliform bacteria in the feces. And, what is even more interesting, some of these condensed derivatives were shown to be active in the presence of ulcerations of the mucosa. The presence of the free carboxyl group influences the excretion of compounds of this series by the biliary tract (unpublished data).

In this study the bacteriostatic activity of sulfanilamide and various derivatives and combinations of these compounds (18 drugs in all) was

4. Woods, D. D.: The Relation of Para-Aminobenzoic Acid to the Mechanism of the Action of Sulfanilamide, Brit. J. Exper. Path. **21**:74, 1940.

5. Miller, E.; Rock, H. J., and Moore, M. L.: Substituted Sulfanilamides: I. N^4-Acyl Derivatives, J. Am. Chem. Soc. **61**:1198, 1939.

investigated; the results of these experimental studies on dogs are summarized in table 1. From this table it is evident that succinylsulfanilamide and succinylsulfathiazole may be expected to have useful therapeutic applications. The results of these studies on both the experimental animal and on man can best be discussed under three heads: (1) antibacterial activity as shown by the effects on the coliform organism in the stool, (2) absorption and excretion and (3) toxicity.

MATERIALS AND METHODS

Routine Experimental Approach Used in the Study of Each Compound.—Dogs were used exclusively for the feeding experiments. After withholding food for twenty-four hours, a specimen of stool was taken directly from the rectum for a bacterial count. The drug was then given every four hours. The total quantity to be administered in twenty-four hours was weighed and mixed thoroughly with freshly ground meat. This meat was divided into six equal portions and comprised the entire food ration for the animal. Thus the animal received the drug thoroughly mixed with a low residue diet at four hour intervals: 12 m., 4 p. m., 8 p. m., 12 a. m., 4 a. m. and 8 a. m. A stool specimen was taken directly from the rectum daily at 10 a. m. Blood was taken from an ear. Urine was obtained directly by catheterization to avoid contamination with the drug from the highly concentrated feces.

Experience has shown that the first sign of intoxication in the dog is anorexia. If, after the animal has refused to eat, it is forcibly fed, other toxic manifestations may occur, such as vomiting, loss of weight, bloody stools, erythematous rash, conjunctivitis, photophobia, liquefaction of the cornea, irritability, tetany, paralysis and, finally, death. Once an animal had accepted the drugged food, so that refusal because of the taste of the compound or because of the animal's feeding habits was excluded, its failure to eat was considered an early sign of toxicity. The quantity of meat given never exceeded the animals's food requirements.

If the trial daily dosage of 1.0 and 0.5 Gm. per kilogram of body weight in six divided doses gave evidence of good bacteriostatic properties, the efficacy of the drug was further studied with dosages of 0.25, 0.1 and 0.05 Gm. per kilogram per day. In this manner the smallest effective dose was determined and the therapeutic ratio indicated.

Those drugs which gave promise of suitable properties were fed over long periods for studies of chronic toxicity. Finally, extensive gross and microscopic examinations of the tissues were made.

Quantitative Determination of the Drug.—The quantitative estimation of the drug content of the blood, the urine and the stool followed the method of Bratton and Marshall,[6] which was modified when necessary. Some of the dibasic condensation products are difficult to hydrolyze and frequently require alkaline saponification to free the aromatic amino radical to permit diazotization and subsequent coupling to form the dye for colorimetry. An Evelyn colorimeter was used.

The percentage of drug in the stools is expressed on the basis of the water content of the excreta. A specimen of stool is weighed, dried in a vacuum and

6. Bratton, A. C., and Marshall, E. K., Jr.: A New Coupling Component for Sulfanilamide Determination, J. Biol. Chem. **128**:537, 1939.

TABLE 1.—*Comparison of the Absorption, Excretion and Toxicity and the Bacteriostatic Activity of Sulfanilamide and a Series of Its Derivatives, as Indicated by the Local Effects on the Coliform Bacteria in the Bowel of the Dog*

Compounds	Daily Doses	Total Daily Dose, Gm. per Kg.	Concentration of the Drug in the Blood, Mg. per 100 Cc.		Concentration of the Drug in the Urine, Mg. per 100 Cc.		Drug Contents of the Stool (Gm. per 100 Cc. Based on Water Content of Feces)	Comparative Antibacterial Action	Toxicity	Comments
			Free	Conjugated	Free	Conjugated				
Sulfanilic acid	2	1.5	18.0	22.0	...	...	Saturated	±	++	Readily absorbed, giving high blood levels with relatively little effect on coliform organisms in bowel
	2	1.0	10.0	10.0	...	...	Saturated	±	++	
Sulfanilamide	6	0.25	12.0	....	...	...	0.55	++	0	Some effect on coliform bacteria, but not sufficient even at toxic levels of drug
	6	0.5	30.0	....	...	...	0.60	++	0	
	6	1.0	50.0	....	...	...	....	++	++++	
Sulfadiazine	6	1.0	45.0	....	...	...	0.21	++	++	Local action insignificant in dosages causing toxic manifestations
Sulfathiazole	6	0.25	15.0	....	Crystals		....	0	+	High blood levels of drug without local action
Sulfanilylguanidine	6	0.3	5.0	....	...	...	5.0	++	0	1 Gm. per kilogram per day in six equally divided doses causes moderate drop in coliform organisms in bowel; concentration of drug in blood moderately high; urine saturated; toxic manifestations severe in a large percentage of animals with occurrence of corneal lesions
	6	1.0	10 to 15	....	Saturated crystals		Solid drug	++	+++	
	2	5.0	10 to 15	....	Saturated crystals		Solid drug	+++	++++	
	5	5.0	10 to 35	....	Saturated crystals		Solid drug	++	++++	
Maleylsulfanilamide	6	0.25	2	2.0	...	500	....	±	++++	Highly toxic, producing anorexia, diarrhea, vomiting, paralysis and death; death may occur after few days; with small doses animals become paralyzed and die weeks after discontinuance of drug
	6	0.5	3	3.0	...	660	....	+++	++++	
	6	1.0	....	....	...	...	....	++++	++++	
Maleylsulfanilhydroximide	2	5.0	....	....	...	...	....	+++	++++	Highly toxic, causing vomiting, bloody diarrhea, nephritis and death
Succinylsulfanilamide	6	0.25	2.5	1.6	210	960	...	+	0	Low toxicity; anorexia and vomiting occur with higher dosage levels; causes no deaths; all animals recover immediately after dosage is lowered; high antibacterial activity; animals healthy after 7 weeks' dosage of 1 Gm. per kilogram daily; no tissue lesions occur
	6	0.5	2.5	1.0	...	...	5.0	++	0	
	6	1.0	4.0	1.5	350	2,400	5.0	++++	0	
	6	2.0	2.5	1.5	...	...	...	++++	++	
	6	5.0	2.5	0.5	...	...	4.0	++++	++	
Succinylsulfanilamide and sulfanilamide	6	0.25*	2.5	0	...	...	...	....	....	Action of succinylsulfanilamide somewhat enhanced by simultaneous administration of sulfanilamide
	6	0.25†	2.5	0	...	...	2.5	++	0	
	6	0.5*	2.5	2.5	...	...	5.0	++++	0	
	6	0.25†								

	6	0.5*	2.5	2.5	...	...	5.0	++++	0	sulfanilamide
	6	0.25†								

Succinylsulfanilamide and sulfadiazine	6	0.5	....	....	...	...	...	....	....	Simultaneous administration of sulfadiazine with succinylsulfanilamide enhances activity of latter; blood concentration becomes rather elevated
	6	0.5	45	4.0	...	...	8.0	++++	0	
Succinylsulfanilhydroxamide	2	0.5	....	....	...	...	...	++	++++	Extremely toxic, causing bloody diarrhea and extensive gastroenteritis
	6	0.5	....	....	...	...	...	0	++++	
Succinylsulfathiazole	6	0.05	2	4	65	170	5.0	+	0	Low toxicity; only toxic manifestation observed was anorexia after high dosages; animals receiving 1 Gm. per kilogram daily for 5 weeks showed no evidence of toxicity; during this entire period coliform bacteria were at extremely low levels; extensive tissue studies revealed no abnormalities
	6	0.1	3	5	80	270	6.0	++	0	
	6	0.25	4	4	125	560	6.0	++	0	
	6	0.5	3	4	180	600	5.0	+++	0	
	6	1.0	3.5	5	360	600	5.0	++++	0	
	6	2.0	3.5	7	250	600	5.0	++++	+	
Sulfathiazole and succinylsulfathiazole	6	0.25‡	....	....	...	...	...	....	....	Simultaneous administration of sulfathiazole with succinylsulfathiazole augments effect on coliform organisms in bowel (chart 5); some toxicity due to relatively high concentration of sulfathiazole in blood
	6	0.10§	11.4	0.4	...	...	5.3	++	+	
	6	0.25‡	13.2	1.83	...	...	6.0	+++	+	
	6	0.25§								
	6	0.25‡	12.0	1.4	...	...	6.5	++++	+	
	6	0.50§								
Succinylsulfanilamidoethylthiazolidone	6	0.5	....	6	...	...	...	+++	+++	Moderately toxic; anorexia develops by third day; compound has fair degree of antibacterial activity
	6	1.0	....	10	...	...	...	+++	+++	
	6	2.0	....	4	...	220	5.0	++	+++	
Succinylsulfapyridine	6	0.5	....	4	...	...	...	+++	+++	While this drug has moderate antibacterial activity, it is too toxic for large doses
	6	1.0	....	33	...	1,305	3.7	+++	+++	
Succinylsulfadiazine	6	0.5	....	....	...	...	...	++	++	Too toxic at doses having antibacterial activity
	6	1.0	....	....	...	...	...	+++	++	
	6	2.0	....	....	...	...	...	+++	++	
Succinylsulfanilylguanidine	6	0.05	....	....	...	...	...	0	0	While this drug has exhibited no toxicity under the conditions studied, it does not appear to be a satisfactory compound, because even though it promptly reduces the coliform count, it fails to keep the count down; after a week the effect completely disappears
	6	0.10	....	....	...	...	...	0	0	
	6	0.25	....	....	...	...	...	0	0	
	6	0.50	....	....	...	...	...	+++(?)	0	
	6	1.0	....	....	...	...	...	+++(?)	0	
Succinylsulfamethyldiazine	6	0.5	....	....	...	...	...	+	0	Low toxicity; antibacterial activity not pronounced
	6	1.0	....	....	...	...	...	++	0	

* Succinylsulfanilamide.
† Sulfanilamide.
‡ Sulfathiazole.
§ Succinylsulfathiazole.

reweighed. The difference in weight gives the quantity of water. The dried stool is suspended in water, and the drug content of an aliquot part is determined.

$$\frac{\text{Weight of the drug in the stool}}{\text{Weight of the water in the stool}} \times 100 = \text{Percentage of the drug based on the water content of the stool}$$

This notation is used because the quantity of the drug compared with the water content of the stool determines the degree of saturation. There is a wide variation in the water content because an effective drug of this series modifies the stool considerably.

Bacteriologic Studies.—Stool specimens were taken at frequent intervals directly from the rectum of the experimental animal and from the freshly expelled feces of the patient. It is important that the stool specimens be chilled immediately and kept cold, because once the feces are expelled, the bacteria might multiply rapidly at room temperature. A quantity of feces which, depending on its consistency, would give approximately 1 cc. of sediment was emulsified and suspended in 10 cc. of sterile physiologic solution of sodium chloride and then centrifuged for fifteen minutes at a speed of 1,700 revolutions per minute. The amount of sediment was read, and dilutions were made based on this value. One cubic centimeter of sediment was considered equivalent to 1 Gm. of wet stool. All counts were made on pour plates. Desoxycholate agar was used for differentiating Bacillus coli, and plain infusion broth agar plates were employed for making total aerobic bacterial counts.

B. coli, Bacillus proteus, Bacillus pyocyaneus, Aerobacter aerogenes and Streptococcus faecalis can be identified in the desoxycholate agar medium. No further identification was practical. The drugs which possess the greater bacteriostatic activity frequently caused the total number of aerobic bacteria to decrease by more than the mere drop due to the fall in the number of coliform organisms. Ordinarily the number of aerobic bacteria would be one thousand to ten thousand times that of B. coli.

It is interesting to note that as the B. coli flora decreased to low numbers, B. proteus frequently began to grow out, increasing at times to 1,000 to 10,000 colonies per gram of wet stool. A. aerogenes would occasionally grow out as B. coli disappeared. This phenomenon causes considerable confusion because the appearance of the deep colonies of these two strains of organisms in the desoxycholate medium is identical. An attempt was made to count these bacteria differentially by the ratio of the surface colonies, which are distinguishable by their characteristic growth.

OBSERVATIONS ON SUCCINYLSULFANILAMIDE [5]

Table 1 shows succinylsulfanilamide to have excellent bacteriostatic activity and low toxicity. This compound has a solubility of 3.5 Gm. per hundred cubic centimeters of water at 20 C. Dogs receiving this drug in sufficient amount to cause excellent lowering of the coliform organisms show average blood levels of 2.5 mg. per hundred cubic centimeters for sulfanilamide and 1.5 mg. per hundred cubic centimeters for succinylsulfanilamide. The concentrations in the urine, however, reach 350 and 2,400 mg. per hundred cubic centimeters, respectively. Since these concentrations are less than the solubilities of these compounds in the urine, no crystals are present. Animals receiving 2 to 5

Gm. per kilogram daily at four hour intervals show mild toxic symptoms of anorexia and vomiting. Two animals were fed 1 Gm. per kilogram daily in six divided doses for ninety-five days. The stools of these animals were practically free of coliform organisms for this period, and toxic manifestations did not develop. Extensive examination of the tissues, both gross and microscopic, revealed no abnormalities.

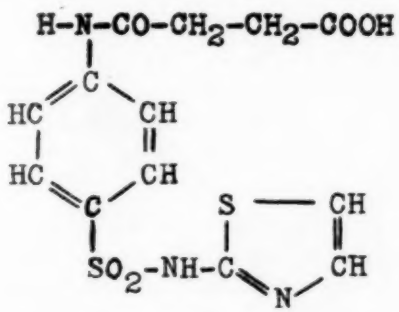
The effect of the simultaneous administration of sulfanilamide and succinylsulfanilamide was studied. The conclusion was that the addition of sulfanilamide did not appreciably enhance the local action of the succinyl derivative.

Succinylsulfanilamide was administered to 3 patients in a dosage of 0.15 Gm. per kilogram daily in six divided doses. The blood levels averaged 2.0 mg. of succinylsulfanilamide per hundred cubic centimeters, and a maximum of 15.0 per cent of the ingested drug was excreted in the urine by 1 patient. With this dosage there was no appreciable effect on the coliform bacteria in the stools. Because of the relatively high absorption of the drug, its use was abandoned, although no toxic symptoms had developed.

OBSERVATIONS ON SUCCINYLSULFATHIAZOLE

Preliminary experimental studies showed succinylsulfathiazole to be most promising. It has strong antibacterial action, is poorly absorbed from the gastrointestinal tract and has not produced toxic manifestations when given in therapeutic doses.

N^4-succinylsulfathiazole [7] may be represented as follows:



It has a solubility of 70 mg. in 100 cc. of water at 37 C. The solubility in urine obviously varies considerably with the p_H and the buffer capacity of an individual specimen because of the readiness with which the free carboxyl group enters into salt formation. The compound is a relatively strong acid, decomposing sodium bicarbonate in aqueous solution. The

7. N^4-succinylsulfathiazole is registered under the proprietary name of sulfasuxidine by Sharp & Dohme, Philadelphia.

sodium salt is highly soluble. A syrupy 50 per cent aqueous solution of the sodium salt will crystallize after standing for seven to ten days at 0 C. The succinic acid radical is split off with difficulty, requiring two hours' digestion on a water bath in half-molar sodium hydroxide to effect quantitative saponification and liberation of the primary amino group. A 25 per cent aqueous solution of the sodium salt is stable; it showed no appreciable hydrolysis after six weeks at 37 C.

Activity in Vitro.—Dr. W. Barry Wood compared this compound with sulfanilamide and some of its derivatives as regards their bacteriostatic activity in vitro against a standard strain of B. coli in a synthetic medium and found the following approximate relations:

Sulfanilamide	1 (unit)
Sulfanilylguanidine	2
Succinylsulfathiazole	0.1
Sulfapyridine	20
Sulfadiazine	20
Sulfathiazole	50

Furthermore, paraaminobenzoic acid completely inhibits the bacteriostatic activity of succinylsulfathiazole. The activity in vitro shown might have been due to the presence of a small amount of free sulfathiazole in the sample studied. Theoretically, unaltered succinylsulfathiazole should have no activity in vitro.

Antibacterial Activity in the Gastrointestinal Tract.—The bacteriostatic activity of succinylsulfathiazole as measured by its effect on the coliform organisms of the bowel has been studied with varying dosages (table 1) in 35 dogs. When given in adequate amounts, succinylsulfathiazole has not failed to lower the coliform count significantly. The character of the stools changes greatly. They become soft, contain undigested food, have a gelatinous appearance and are practically odorless. Diarrhea is not present. Chart 1 shows the characteristic effects with various dosages.

To study the effect of the presence of ulcerating lesions in the bowel on the bacteriostatic properties of the drug, sloughing lesions were produced in the colon through the destruction of large areas of mucous membrane with liquid phenol by proctoscopy. The drug was equally effective in the presence of these lesions (chart 2).

The simultaneous oral administration of sulfathiazole, which is readily absorbed, and succinylsulfathiazole, which is sparingly absorbed, produces an effect which appears to be a synergistic action of the two drugs (table 1 and chart 3).

Absorption and Excretion.—Since the toxic manifestations of any particular compound must be due not merely to the concentration attained

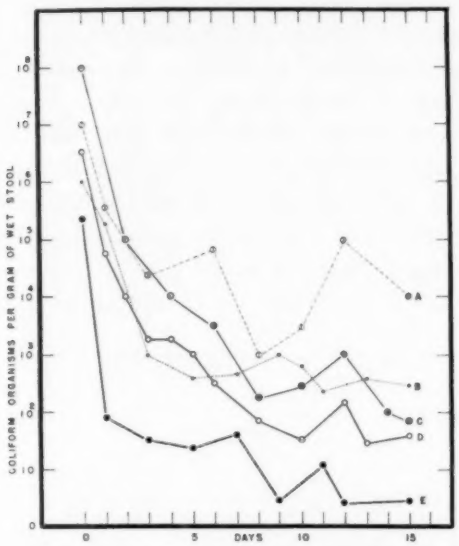


Chart 1.—The effect of various dosages of succinylsulfathiazole on the coliform bacteria in the gastrointestinal tract of the dog. Each curve is based on the average effects observed in from three to five experiments. *A* represents the results after the oral administration of 0.05 Gm. per kilogram daily, given in six equal doses at four hour intervals; *B*, 0.1 Gm. per kilogram; *C*, 0.25 Gm. per kilogram; *D*, 0.5 Gm. per kilogram; *E*, 1.0 Gm. per kilogram.

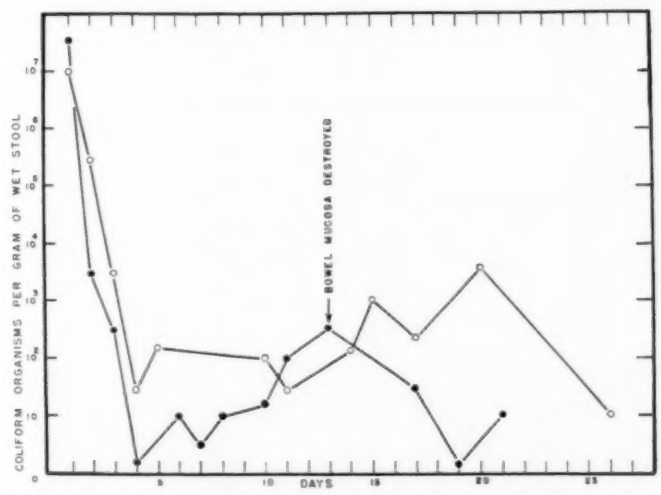


Chart 2.—To demonstrate the effect of lesions of the mucous membrane on the antibacterial activity of succinylsulfathiazole, the number of coliform organisms was reduced by the administration of the drug. Then the mucosa of a large area of the descending colon of the dog was destroyed by cauterization.

in the blood and tissues but also to the absolute quantity absorbed from the gastrointestinal tract and excreted by the kidneys after oral administration, the concentration and the amount of the drug excreted in the urine must be observed (charts 4 and 5). The concentration of the drug in the urine can be determined from specimens obtained directly from the bladder by catheterization, but the total urinary output of the drug over a period cannot be estimated readily because of inability to collect the urine without contamination by feces containing relatively much larger quantities of drug (table 1). One must therefore be content with the determination of the urinary concentration as a guide in the

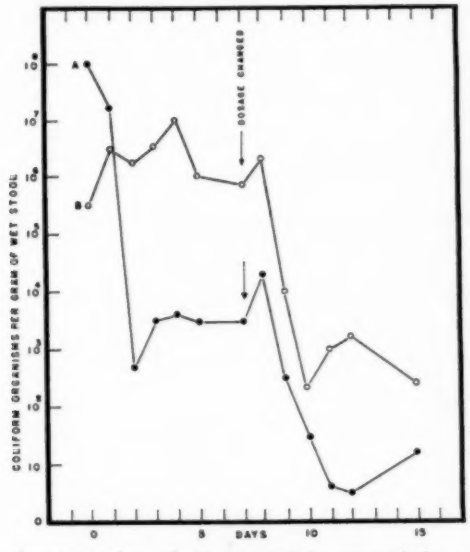


Chart 3.—A demonstration of the apparently synergistic action of sulfathiazole and succinylsulfathiazole when simultaneously administered to the dog. *A* received daily 0.25 Gm. of succinylsulfathiazole per kilogram in six doses for seven days. At this time a daily dose of 0.25 Gm. of sulfathiazole per kilogram was added. *B* received 0.25 Gm. of sulfathiazole per kilogram daily for seven days; then succinylsulfathiazole was added so that the animal thereafter took 0.25 Gm. per kilogram of each drug daily.

experimental animal and must reserve the quantitative output of the drug to be determined on patients receiving the compound after it has been proved otherwise suitable for human use. On an average, a dog receiving 1 Gm. per kilogram daily in six divided doses will have a concentration of 3.5 mg. per hundred cubic centimeters for sulfathiazole and 5.0 mg. per hundred cubic centimeters for the conjugated compound in the blood, while the respective concentrations in the urine are 360

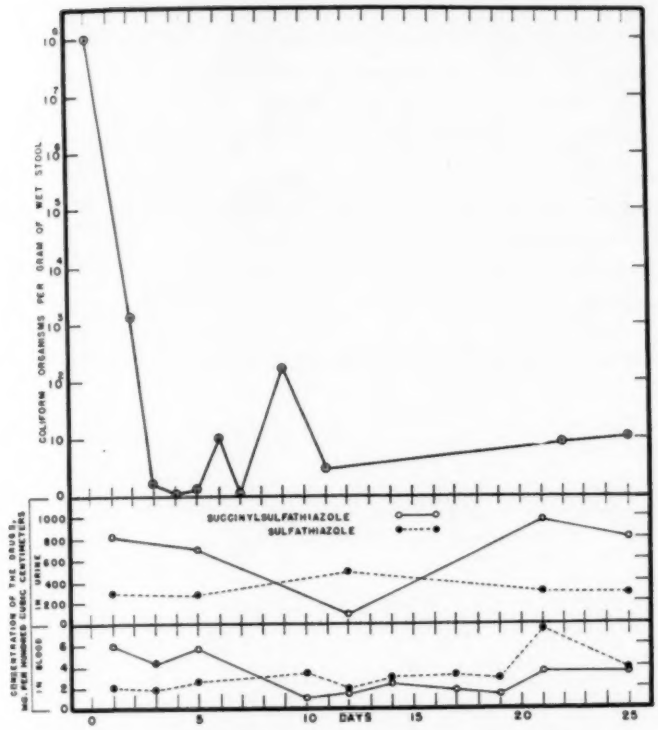


Chart 4.—The significant lowering of the number of coliform bacteria in the bowel of the dog after the daily oral administration of 1 Gm. per kilogram of succinylsulfathiazole divided into six equal doses. The concentrations of the drug in the blood and the urine are given. The degree to which hydrolysis of succinylsulfathiazole is effected to yield sulfathiazole is indicated by the concentration of the latter in the blood and the urine.

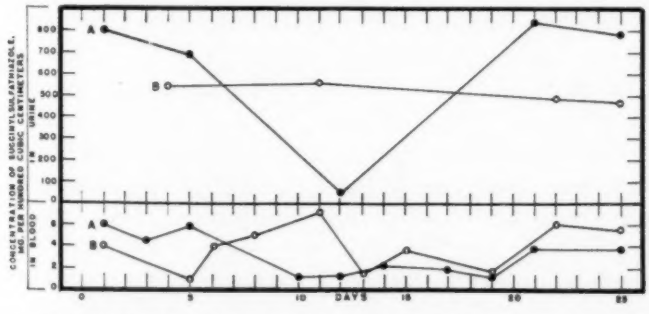


Chart 5.—Illustration of the fact that an animal (*A*) receiving daily 1 Gm. of succinylsulfathiazole per kilogram divided into six equal oral doses has essentially the same concentration of the drug in its blood and urine as another animal (*B*) similarly receiving a dosage of 0.25 Gm. per kilogram.

and 600 mg. per hundred cubic centimeters. With this dose the concentration in the stools will average 5 per cent (table 1).

Toxicity in the Dog.—This drug and its sodium salt are so poorly absorbed that, regardless of the dose, no acute toxicity can be demonstrated after oral administration. The acid is rapidly absorbed from the peritoneal cavity, and after intramuscular administration, although the concentration of the drug in the blood is considerable, no toxic manifestations occur (charts 7 and 8). There is some local tenderness after intraperitoneal and intramuscular injection of a water suspension of the solid drug. Laparotomy done a few days after intraperitoneal

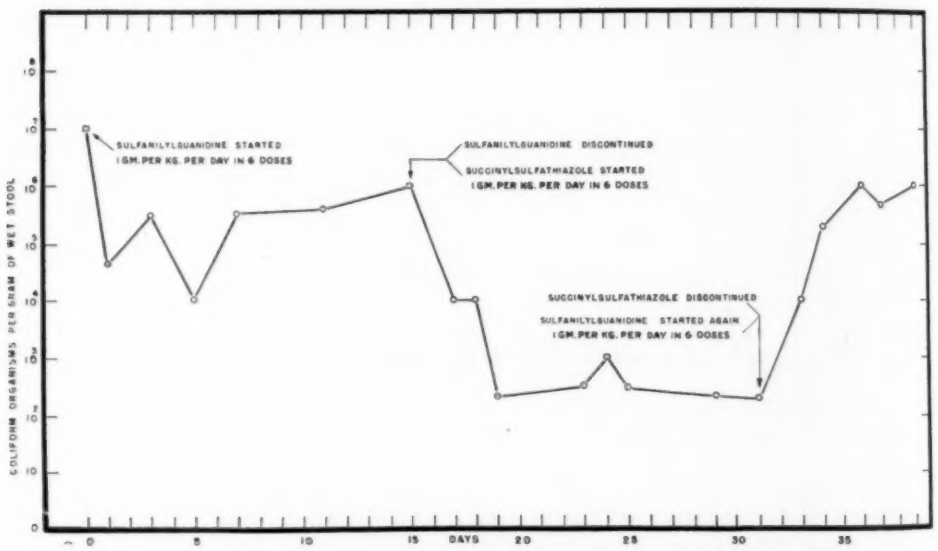


Chart 6.—The relative antibacterial activity of sulfanilylguanidine and succinylsulfathiazole as demonstrated by the effects of these drugs on the coliform organisms in the bowel of the dog.

administration shows the peritoneal cavity to be normal and free of adhesions.

The monosodium salt of succinylsulfathiazole in solution suitable for intravenous administration is readily prepared by the addition of the stoichiometric quantity of sodium bicarbonate to the free acid, succinylsulfathiazole.

Five grams per kilogram of succinylsulfathiazole converted to the sodium salt and given intravenously as a 40 per cent solution causes vomiting in about three to five minutes followed by defecation and collapse. Tetanic seizures accompanied by deep cyanosis develop shortly. This dose is fatal in two hours. At necropsy the concentration

of the free drug in the blood is 30 mg. per hundred cubic centimeters, and the conjugated compound is present in a concentration of 600 mg. per hundred cubic centimeters.

The intravenous administration to 5 dogs of 1 Gm. per kilogram of the sodium salt in a 15 per cent solution caused nausea, and the animals vomited once after ten to fifteen minutes. No further toxic

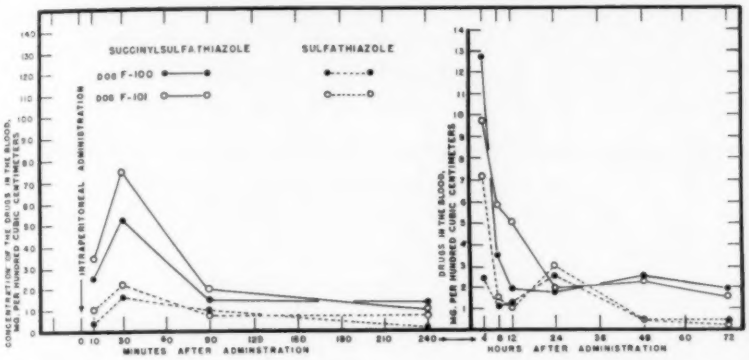


Chart 7.—Illustration of the rapid rate of absorption after the intraperitoneal injection of an aqueous suspension of 1 Gm. per kilogram of succinylsulfathiazole and the rate of its disappearance from the blood.

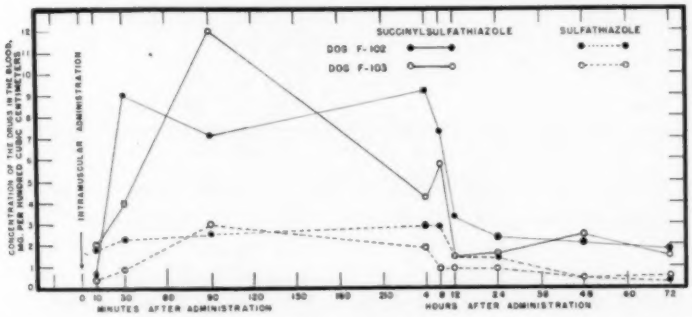


Chart 8.—The concentration of sulfathiazole and succinylsulfathiazole in the blood after the intramuscular administration of an aqueous suspension of 1 Gm. per kilogram of succinylsulfathiazole.

symptoms occurred. The concentration of the drug in the blood and the rate of urinary excretion are presented graphically in chart 9. Complete gross and microscopic examination of the tissues showed no anatomic abnormalities. The intravenous administration of 1 Gm. per kilogram daily for ten days caused the usual vomiting immediately after administration of each dose. Anorexia and increased salivation

sometimes occurred after the second or third dose. The concentration of the drug in the saliva was low, 0.6 mg. per hundred cubic centimeters. These animals showed no additional toxic manifestations. Comparison of specimens of the liver taken before treatment and at necropsy after ten days of repeated daily intravenous injections of 1 Gm. per kilogram of the sodium salt of succinylsulfathiazole showed no histologic changes in the liver cells. The urine sometimes contained as much as 11,000 mg. per hundred cubic centimeters of the drug after intravenous, intraperitoneal and subcutaneous administration of 2 Gm. per kilogram daily of the sodium salt of succinylsulfathiazole for several days. At this high concentration the urine in some cases was clear and had a p_H of

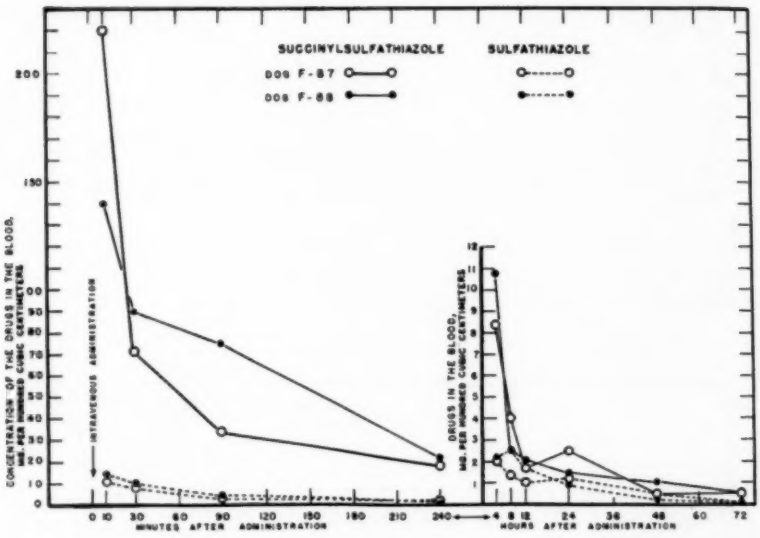


Chart 9.—The rapidity with which the drug disappears from the blood after the intravenous injection of 1 Gm. per kilogram of the sodium salt of succinylsulfathiazole.

6.8. The addition of mineral acid, however, caused the urine to solidify by the precipitation of the relatively insoluble acid form of succinylsulfathiazole.

Dogs receiving 1 Gm. per kilogram daily of succinylsulfathiazole in six divided doses for as long as thirty-five days ate regularly, gained weight and showed no tissue changes on gross and microscopic examination. Concretions of the drug in the kidneys and bladder did not occur. Thirty dogs received the drug in doses as high as 2 Gm. per kilogram daily over a period of several weeks.

Administration to Man.—After obtaining evidence from the laboratory animal indicating the low toxicity and the possible therapeutic

value of succinylsulfathiazole, trial administration of the drug to human beings was undertaken. Normal persons with intact mucous membranes of the gastrointestinal tract were given single doses and then doses of varying amounts at four hour intervals. These persons were kept under close observation, and daily studies of the blood, the urine and the stool were made.

The results of these studies are summarized in table 2. This tabulation shows that the drug is poorly absorbed by man. The quantity of drug excreted in the urine over a period of days varies from 3 to

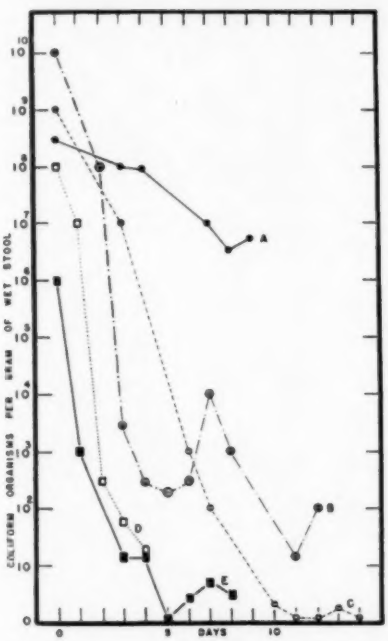


Chart 10.—The effect of varying dosages of succinylsulfathiazole on the coliform bacteria in the gastrointestinal tract of man: *A* diagrams the results of the oral administration of 0.1 Gm. per kilogram divided into six equal doses. *B* represents the effect of the similar administration of 0.2 Gm. per kilogram; *C*, the effect of 0.25 Gm. per kilogram; *D*, the effect of an initial dose of 0.25 Gm. per kilogram followed after four hours by 0.25 Gm. per kilogram per day in six equally divided doses (this patient had large ulcerating carcinoma of the rectum); *E* represents the course after the oral administration of three massive doses of 0.25 Gm. per kilogram at four hour intervals followed by 0.25 Gm. per kilogram per day divided into six equal quantities.

9 per cent of that ingested. On an average 5 per cent of the ingested drug is recovered in the urine.

Examination of chart 10 shows the average therapeutic dose required to alter the bacterial flora of the bowel significantly to be 0.25 Gm. per

TABLE 2.—*Effects of the Oral Administration of Succinylsulfathiazole on Human Beings with Normal Intact Mucous Membranes of the Gastrointestinal Tract*

Patient and Weight, Kg.	Day and Time	Daily Dose Given in Six Equal Fractions, Gm.	Concentration of Drug in Blood		Daily Urinary Output, Gm.		Concentration of Drug in Stools, Gm. per 100 Cc.	Comment
			Free	Conjugated	Free	Conjugated		
N. K. 70	1 8:00	35.00 (in one	....	....	....	....	....	Patient had a normal gastrointestinal tract; he was given a single dose of succinylsulfathiazole equivalent to 0.5 Gm. per Kg.; coliform count dropped from 10^6 to 10^4; 4.8% of ingested drug was excreted in urine; no evidence of toxicity
	12:00	single	1.50	0.90				
	4:00	dose at	1.30	1.60				
	8:00	8 a.m.)	0.96	1.90	....	....	1.30	
	2	....	0.30	1.50	0.47	0.43		
	3	....	0.40	1.00	0.09	0.46	2.00	
	4	....	0.00	0.00	0.00	0.00		
K. A. 61	1	6.00	....	....	0.03	0.02	....	Normal bowel; received 0.1 Gm. per Kg. daily in six divided doses; coliform organisms dropped from 10^8 to 10^6; drop not considered significant; dosage insufficient; 5% of ingested drug excreted in urine; no toxic manifestations
	2	6.00	....	....	0.10	0.08		
	3	6.00	0.80	1.70	0.14	0.22		
	4	6.00	0.50	2.60	0.23	0.10	0.26	
	5	6.00	0.40	1.70	0.12	0.34		
	6	6.00	0.40	2.60	0.03	0.04	0.88	
	7	6.00	....	....	0.20	0.26	1.90	
	8	6.00	0.90	1.90	0.14	0.10		
	9	6.00	....	....	0.14	0.18	1.04	
	10	6.00	0.50	0.80	0.14	0.25	0.60	
	11	....	0.30	0.40	....	....	0.80	
H. L. 50	1	9.00	....	....	0.48	0.60	....	Patient convalescing; normal bowel; received equivalent of 0.18 Gm. per Kg. of succinylsulfathiazole daily; coliform count in stools dropped from 10^7 to 15 colonies per Gm. of wet stool and was maintained at a low level for six days; no toxic manifestations; 9.05% of ingested drug was excreted in urine
	2	9.00	0.80	8.00	0.30	1.70	0.60	
	3	9.00	0.84	6.50	0.14	0.13	0.56	
	4	9.00	1.30	4.50	0.16	0.16	0.60	
	5	9.00	1.30	3.00	0.35	0.40	2.70	
	6	9.00	1.30	3.60	0.19	0.16	3.30	
	7	9.00	0.80	7.40	0.23	0.14		
	8	0.00	0.80	1.70	0.11	0.09	0.36	
	9	0.00	0.80	1.80	0.12	0.00	0.43	
	10	9.00	2.40	7.30	0.44	0.19	0.57	
	11	9.00	....	....	0.22	0.22	0.84	
	12	9.00	1.00	2.30	0.23	0.07	3.88	
	13	9.00	0.80	1.40	0.27	0.56	1.49	
G. B. 83	1	16.50	2.90	2.00	0.23	0.28	....	Postoperative hernia; normal gastrointesinal tract; received equivalent of 0.2 Gm. per Kg. succinylsulfathiazole daily; stool count for coliform bacteria dropped from 10^9 to 0 and remained below 10 for last 6 days that patient was under observation; 5.33% of ingested drug excreted in urine; no toxic manifestations
	2	16.50	2.00	2.50	0.25	0.40		
	3	16.50	2.20	0.50	0.19	0.38	1.10	
	4	16.50	0.80	7.30	0.16	0.33		
	5	16.50	0.80	1.20	0.37	0.91		
	6	16.50	....	....	0.16	0.23	2.80	
	7	16.50	0.80	1.20	0.26	0.43	5.06	
	8	16.50	0.80	1.20	0.18	0.39		
	9	16.50	0.50	2.30	0.22	0.57		
	10	16.50	0.80	1.70	0.73	0.73	6.51	
	11	16.50	1.30	4.30	0.38	0.78	3.05	
	12	.....	1.20	1.40	....	....	3.00	
	13	.....	....	....	....	....	6.50	
R. E. 60	1	36.00 (at 8 a.m.)	....	....	....	....	....	Normal gastrointestinal tract; given initial dose of 0.5 Gm. per Kg. followed by maintenance dosage of 0.2 Gm. per Kg. daily; coliform bacteria count dropped to 50 organisms per Gm. of wet stool; 3.5% of ingested drug was excreted in urine; no toxic manifestations
	12:00	.....	1.30	2.10				
	4:00	.....	0.80	1.40				
	8:00	.....	1.00	3.90	0.20	0.33	3.00	
	2	12.00	0.80	3.50	0.16	0.39	9.20	
	3	12.00	0.50	3.30	0.57	0.16	2.90	
	4	12.00	1.10	2.10	0.41	0.26	1.00	
	5	12.00	1.30	1.90	....	....	1.90	
	6	12.00						
L. Y. 75	1	44.00	....	....	0.35	0.12	....	Normal bowel; initial dose of 32 Gm., then maintenance dosage of 0.25 Gm. per Kg. per day; B. coli count dropped to 20 organisms per Gm. of wet stool; 4.41% of ingested drug excreted in urine; no toxic manifestations
	2	18.00	1.00	1.20	0.46	0.50		
	3	18.00	1.00	1.20	0.36	0.37	0.00	
	4	18.00	0.84	0.87	0.33	0.68	1.20	
	5	18.00	0.42	1.00	0.41	0.39	9.10	
	6	18.00	0.42	2.80	0.53	0.43	6.30	

TABLE 2.—*Effects of the Oral Administration of Succinylsulfathiazole on Human Beings with Normal Intact Mucous Membranes of the Gastrointestinal Tract—Continued*

Patient and Weight, Kg.	Day and Time	Daily Dose Given in Six Equal Fractions, Gm.	Concentration of Drug in Blood		Daily Urinary Output, Gm.		Concentration of Drug in Stools, Gm. per 100 Cc.	Comment
			Free	Conjugated	Free	Conjugated		
T. Y. 70	1	9.00	....	....	....	....	....	Normal bowel; given 0.25 Gm. per Kg. daily; the B. coli count dropped from 10^9 to 100 per Gm. of wet stool; 5.2% of ingested drug excreted in urine; no toxic manifestations
	2	18.00	0.39	0.51	0.22	0.25		
	3	18.00	0.80	1.40	0.68	0.80	4.40	
	4	18.00	0.60	1.70	0.40	0.52	2.90	
	5	18.00	....	....	0.67	1.06	6.80	
	6	18.00	1.08	0.80	0.30	0.43	1.60	
	7	18.00	1.00	4.00	0.32	0.33	1.70	
	8	18.00	0.50	2.40	0.30	0.36		
	9	18.00	1.20	1.05	0.37	0.34		
	10	18.00	0.80	1.20	0.30	0.40		
	11	18.00	0.80	1.20	0.20	0.20	3.60	
	12	18.00	0.40	1.70				
M. R. 75	1	69.00	....	....	0.46	1.07	....	Normal bowel; received 0.75 Gm. per Kg. during first eight hours of administration of drug; there was no marked elevation of blood level of drug; B. coli count dropped from 10^8 to 115 per Gm. of wet stool; there were no toxic manifestations; 4.5% excreted in urine
	2	18.00	1.30	1.80	0.26	0.44	8.83	
	3	18.00	1.40	0.50	0.46	1.58	13.90	
	4	18.00	1.00	1.40	....	....	12.20	
	5	18.00	0.12	2.70	....	....	5.70	
T. N. 64	1	23.50	....	....	0.25	0.26	0.20	Normal bowel; received an initial dose of 0.25 Gm. per Kg. followed by 0.25 Gm. per Kg. per day in six divided doses; coliform organisms dropped from 10^9 to as low as 300 per Gm. of wet stool; 5.5% of ingested drug was excreted in urine
	2	15.00	2.60	3.10	0.94	0.88		
	3	15.00	1.50	1.80	0.22	0.25	0.72	
	4	15.00	1.50	3.20	1.84	0.27	3.00	
	5	15.00	0.90	2.20	0.13	0.22		
	6	15.00	0.90	2.20	0.20	0.30		
	7	15.00	....	....	0.30	0.42	8.40	
	8	15.00	0.40	1.40	0.17	0.35	5.10	
	9	15.00	....	....	0.15	0.35		
	10	15.00	0.60	1.50	0.34	0.61		
	11	15.00	1.00	1.60	0.39	0.29	4.30	
	12	15.00	....	....	0.15	0.20		
	13	15.00	0.60	1.40	0.96	0.80	6.60	
	14	15.00						
C. M. 42	1	9.25	....	....	0.14	0.04	0.00	Normal bowel; received 0.25 Gm. per Kg. and an initial dose followed by a maintenance dose of 0.25 Gm. per Kg. daily in six doses; the coliform organisms dropped from 10^9 to 10^5; although this is a 10,000 fold drop, it is not a satisfactory result; an explanation for this failure is not apparent; 6.4% of ingested drug was excreted in urine; no toxic manifestations
	2	10.50	....	....	0.40	0.13		
	3	10.50	0.10	1.70	0.09	0.13	5.50	
	4	10.50	....	....	0.04	0.04		
	5	10.50	0.20	0.60	0.11	0.16		
	6	10.50	0.40	1.50	0.35	0.31	1.67	
	7	10.50	....	....	0.43	0.46		
	8	10.50	0.60	0.60	0.56	0.58		
	9	10.50	....	....	0.03	0.04		
	10	10.50	3.60	0.87	0.72	0.59		
	11	10.50	....	....	0.26	0.21		
	12	10.50	0.40	1.60	0.82	0.65		
	13	10.50	....	....	0.27	0.55		
	14	10.50	1.30	0.00	1.10	0.07		

kilogram per day, administered orally in six equal quantities at four hour intervals. Experience has shown this to be the minimum dose which can be expected to give significant lowering of the coliform bacteria. The routine procedure adopted consists of administering 0.25 Gm. per kilogram in a single initial dose followed by 0.25 Gm. per kilogram daily as stated before. This amount will cause significant lowering of the coliform count of the stools in one to seven days.

Obviously, the effective dose will vary with the condition of the bowel, and it is frequently advantageous to administer 0.5 Gm. per kilogram daily. As much as 1 Gm. per kilogram daily has been given to patients with severe dysentery without ill effects. The administration of 0.25 Gm. per kilogram daily, but given at one hour intervals, did not accelerate the rate of lowering of the coliform bacteria in the stools. However, this frequency of administration did increase the quantity of the drug absorbed and excreted to about twice the amount observed when the same total amount of drug was given at four hour intervals.

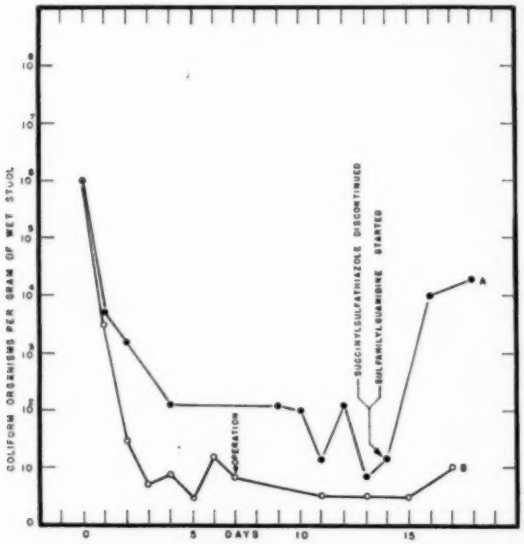


Chart 11.—The relative antibacterial activity of succinylsulfathiazole and sulfanilylguanidine as demonstrated by the effects of these drugs on the coliform organisms in the bowel of man after oral administration. *A* received 0.25 Gm. of succinylsulfathiazole per kilogram daily in three equal doses for fourteen days. This dosage was discontinued, and the maximum recommended dosage of sulfanilylguanidine, 2 Gm. every four hours, was started immediately. *B*, after receiving 10.5 Gm. of sulfanilylguanidine daily for fourteen days had 1,000,000 B. coli per gram of wet stool as indicated on day O of the chart. The curve indicates the course after the daily oral administration of 0.33 Gm. per kilogram of succinylsulfathiazole. *A* had an intact normal gastrointestinal tract; *B* was suffering from chronic ulcerative colitis.

As the bacterial flora is altered by the action of the drug, the character of the feces changes. The stools become semifluid. Ordinarily, diarrhea does not occur. The feces become relatively odorless and contain more than the normal quantity of mucus. The bulk of fecal material is markedly reduced.

Certain conditions existing in the bowel appear to modify the action of succinylsulfathiazole in the bowel. It has been observed that excessive diarrhea or extreme constipation with hard bulky stools interferes with the action of the drug. Liquid petrolatum in the bowel definitely reduces the efficacy of the compound. If the specimens of feces are incubated or left at room temperature, even though the feces are intimately mixed with the drug, the bacterial count of some of the specimens mounts rapidly. In searching for an explanation of the favorable influence of these rather widely different conditions on the growth of bacteria or, rather, of their inhibition of the bacteriostatic activity of succinylsulfathiazole, the following hypothesis can be put forth: If under normal conditions the bowel absorbs paraaminobenzoic acid-like split products, which act as inhibitors, from the stools, which have become semifluid as a result of the administration of the drug, this fact would explain the inhibition of the action of the drug in the four conditions cited: (1) diarrhea—the bowel mucosa does not favor absorption but rather favors excretion of fluid into the lumen; (2) constipation—the material within the inspissated feces does not come in contact with the absorbing surface; (3) liquid petrolatum—the fecal material does not come into intimate contact with the absorbing mucosa; (4) expelled feces—the split products accumulate and inhibit the action of the drug.

Action in the Presence of Ulcerating Lesions of the Gastrointestinal Tract.—While the results of the treatment of human beings with ulcerating lesions of various types will be the subject of a subsequent communication, it is appropriate here to discuss the antibacterial activity of succinylsulfathiazole in the presence of ulcerating lesions of the bowel. If the lesion is extensive, there seems to be a slight delay in the rate at which the bacterial flora is decreased, and on an average the count remains somewhat higher than that observed when the mucosa of the bowel is intact. This phenomenon may necessitate a larger dose of the drug to effect the desired result. There is no evidence that the presence of such lesions in the bowel appreciably alters the absorbability of the drug.

COMMENT

A series of derivatives of sulfanilamide which contain a free carboxyl group has been studied. The primary aromatic amino group has been condensed with a carboxyl group to form a substituted acid amide. This condensation alters their absorbability from the gastrointestinal tract. Furthermore, the carboxyl group probably influences the absorption and excretion of this series of drugs by the liver. The property causing the high biliary excretion might well influence the action in the upper gastrointestinal tract.

The use of succinylsulfathiazole as an intestinal antiseptic has met with excellent results even in the presence of ulcerating lesions of the bowel. At present one can say definitely that the bacterial flora of the gastrointestinal tract is significantly altered by the administration of succinylsulfathiazole, that the drug does not reach high concentrations in the blood, that approximately 5 per cent of the therapeutic oral dose is excreted by the kidneys and that the toxicity of the drug is relatively low. What may be the final clinical advantage to be derived from the lowering of the bacterial count or the interfering with the normal metabolic processes of the bacteria in the gastrointestinal tract before operation remains to be seen after extensive clinical trial and will be the subject of a subsequent communication. Likewise, the results of the use of this drug in the treatment of typhoid fever and bacillary dysentery will be reported later.

Because of the profound alterations in the physical form of the stools and the bacterial flora of the gastrointestinal tract, the effect of the administration of succinylsulfathiazole in the treatment of conditions resulting from chronic intestinal indigestion is worthy of investigation. The cholera vibrio, which is gram-negative and sensitive to an acid environment, might be expected to be vulnerable to the effects of this compound.

Any patient receiving this drug should be under close daily observation for toxic manifestations. The concentration of the drug in the blood and the total urinary output of the drug should be determined. So long as severe toxic reactions due to the administration of this drug are not encountered, its use will be extended.

SUMMARY

Sulfanilamide, derivatives of sulfanilamide and combinations of these compounds have been investigated by oral administration to dogs at four hour intervals. A series of these drugs condensed with dibasic acids to form substituted acid amides has been studied.

Succinylsulfanilamide and succinylsulfathiazole have high bacteriostatic activity as indicated by the effect on the coliform organisms in the gastrointestinal tract of the dog. These compounds have relatively strong acid properties, liberating carbon dioxide from aqueous solutions of inorganic carbonates and bicarbonates.

Succinylsulfathiazole is relatively resistant to chemical hydrolysis. It is split by bacteria to yield sulfathiazole. In vitro it has low bacteriostatic activity against B. coli in synthetic mediums. It is poorly absorbed from the gastrointestinal tract of man. A high concentration of succinylsulfathiazole can be maintained in the gastrointestinal tract of man without causing untoward toxic reactions. It has a high bacteriostatic action in the gastrointestinal tract of man as measured by the

inhibition of the coliform flora of the bowel. The administration of succinylsulfathiazole causes profound changes in the stools. They become semifluid and are rendered relatively odorless. The drug is rapidly excreted by the kidneys. The concentration of the drug in the blood remains low when administered orally. No crystals of the drug have been observed in the urine. The drug administered to human beings has not caused severe toxic reactions. It is excreted by the liver. Succinylsulfathiazole is split by its passage through both man and dog to yield sulfathiazole. The liver appears to be the site where hydrolysis occurs.

A preliminary working dosage of succinylsulfathiazole for man is given. Significant lowering of the coliform organisms in the bowel occurs in over 90 per cent of instances after the administration of succinylsulfathiazole in adequate doses. This drug is effective in the presence of extensive ulcerative lesions of the bowel. The administration of succinylsulfathiazole is suggested for the preoperative preparation of patients requiring operative procedures on the gastrointestinal tract and for the treatment of acute intestinal infections, such as typhoid fever and dysentery. The action of this drug is limited essentially to its local effect on the contents of the gastrointestinal tract.

Dr. J. Howard Brown gave assistance in the bacteriologic studies. Dr. Warfield M. Firor gave encouragement, support and constructive criticism. Sharp and Dohme provided most of the compounds used in this study.

CLINICAL USE OF SUCCINYLSULFATHIAZOLE

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AND
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The experimental basis for the use of succinylsulfathiazole as an agent for altering the flora of the gastrointestinal tract is presented in other papers by us.[1] In those communications the contents of the gastrointestinal tract were described as being profoundly altered by the oral administration of succinylsulfathiazole to experimental animals and man. Such a modification of the intestinal flora suggests the use of this drug especially in the preoperative preparation of the large bowel.

Succinylsulfathiazole has been given to 100 human beings without severe untoward reactions which could definitely be ascribed to its administration. The 100 patients receiving succinylsulfathiazole may be grouped as indicated in table 1.

The knowledge gained from an intensive study of the cases of these patients as it pertains to surgical procedures is the basis for this communication.

LOCAL BACTERIOSTATIC ACTION OF SUCCINYLSULFATHIAZOLE

Succinylsulfathiazole is so poorly absorbed from the gastrointestinal tract that only an average of 5 per cent of the ingested drug is excreted by the kidneys. Its action after oral administration, therefore, is essentially restricted locally to the contents of the bowel. The feces, which contain a moderate amount of mucus, become small in bulk, semifluid and relatively odorless. Ordinarily there will be two to four stools daily without hyperperistalsis or griping pain. Rarely does true diarrhea occur. The bacterial flora is profoundly altered; this is indicated by the effect on the coliform organisms. While the change in the coliform flora is used as an indicator of drug effect, it must be realized that all

This work was aided by a grant from Sharp & Dohme, Inc., Philadelphia.

From the Department of Surgery, Johns Hopkins University School of Medicine.

1. (*a*) Poth, E. J., and Knotts, F. L.: Succinyl Sulfathiazole, a New Bacteriostatic Agent Locally Active in the Gastro-Intestinal Tract, Proc. Soc. Exper. Biol. & Med. **48**:129, 1941. (*b*) Poth, E. J.; Knotts, F. L.; Lee, J. T., and Inui, F.: Bacteriostatic Properties of Sulfanilamide and Some of Its Derivatives: I. Succinylsulfathiazole, a New Chemotherapeutic Agent Locally Active in the Gastrointestinal Tract, Arch. Surg., this issue, p. 187.

organisms in the bowel more susceptible than Bacillus coli to the antibacterial action of succinylsulfathiazole are even more profoundly affected. The Shiga, Flexner and Sonne strains of the dysentery bacillus are especially susceptible to the antibacterial action of this compound. The drug has no apparent effect on the growth of the typhoid and paratyphoid organisms, alpha Streptococcus faecalis or Bacillus proteus. Bacillus aerobacter aerogenes is more resistant than B. coli to the action of succinylsulfathiazole. The change in the character of the stools, including the disappearance of the fecal odor, suggests strongly that the growth of anaerobic proteolytic bacteria is particularly inhibited. A more exhaustive study of the bacteria retarded by this drug is being conducted and will be the subject of a subsequent communication.

TABLE 1.—*Patients Grouped According to Condition*

Group	Condition	Patients
1	Convalescent, with normal intact intestinal mucosa	15
2	Typhoid fever	12
3	Bacillary dysentery	19
4	Diarrhea (nonspecific)	14
5	Carcinoma of the right colon	4
6	Carcinoma of the left colon	15
7	Carcinoma of the transverse colon	2
8	Fecal fistulas involving the colon	3
9	Fecal fistulas involving the small bowel	3
10	Chronic ulcerative colitis	10
11	Diverticulitis	3
	Total	100

MECHANISM OF ACTION

Accurate knowledge of the mode of action of sulfanilamide and its derivatives is as yet lacking. Theoretically, paraaminobenzoic acid or some chemically similar compound combines with a hypothetic substance, possibly an enzyme, to form a metabolite essential to the normal growth processes of certain bacteria. For the sake of simplicity we shall refer to this hypothetic substance as X. It is not known whether X is an endogenous or an exogenous substance as regards the bacterial cells. Fleming [2] showed that dead bacteria added to mediums interfered with the action of sulfanilamide. It is not inconceivable that X may be formed principally by certain strains of bacteria and that it may even be a factor in the phenomenon of symbiosis.

The mechanism and the competitive nature of the reactions of sulfanilamide and its derivatives and paraaminobenzoic acid have been

2. Fleming, A.: Observations on the Bacteriostatic Action of Sulfanilamide and M. & B. 693 and on the Influence Thereon of Bacteria and Peptone, J. Path. & Bact. **50**:69, 1940.

discussed by Woods,[3] Fildes,[4] Lockwood[5] and Wyss.[6] The present concept is that sulfanilamide and its derivatives act because of their tendency to combine with substance X to form a conjugated compound unsuited to the metabolism of bacteria. From this concept it becomes obvious that X is rendered suitable for further metabolic processes depending on whether it is coupled with sulfanilamide or one of its derivatives as expressed by equation 1 or with paraaminobenzoic acid as indicated in equation 2.

Sulfanilamide or one of its derivatives + substance X → Inactive substance (1)
Paraaminobenzoic acid + substance X → Metabolic enzyme or metabolite (2)

The coupling agents will be determined by the concentrations of the competing reactants as governed by the law of mass action and the affinities or natural tendencies of the respective reactions to occur. Thus it is evident that the effectiveness of sulfanilamide or one of its derivatives will be influenced in any given instance not only by the concentration of the drug itself but also by the concentrations of the inhibiting agents and substance X.

Bacteriostasis will be realized in that thermodynamic environment which opposes the formation of the metabolic enzyme or the metabolite necessary for the multiplication of bacteria.

These concepts are particularly interesting with regard to the local bacteriostatic action of succinylsulfathiazole in the bowel. Because of the small bulk and the semifluid character of the feces, the contents of the bowel come into frequent and close contact with the absorbing mucosa. Since it is likely that paraaminobenzoic acid, similar split products and substance X are readily absorbed from the bowel, it can be assumed that the concentrations of these substances, which would favor the formation of the metabolic enzyme, will tend to be lowered and that thus the interaction of sulfanilamide or one of its derivatives and substance X to form a compound unsuitable for enzymatic utilization by the bacteria will be unopposed.

Further understanding of the mode of action of succinylsulfathiazole in the bowel might be forthcoming from an examination of certain conditions unfavorable to the action of the drug.

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3. Woods, D. D.: The Relation of *p*-Aminobenzoic Acid to the Mechanism of the Action of Sulphanilamide, Brit. J. Exper. Path. **21**:74, 1940.

4. Fildes, P.: A Rational Approach to Research in Chemotherapy, Lancet **1**:955, 1940.

5. Lockwood, J. S.: Sulfanilamide and Its Derivatives in Surgical Infections: I. The Mode of Chemotherapeutic Action of the Sulfanilamides, Surgery **10**:493, 1941.

6. Wyss, O.: The Nature of Sulfanilamide Inhibition, Proc. Soc. Exper. Biol. & Med. **48**:122, 1941.

The following facts have been observed:

1. Liquid petrolatum interferes with the antibacterial activity of succinylsulfathiazole.

2. Watery diarrhea due to irritation of the mucosa strongly inhibits the antibacterial action of the drug.

3. Hard constipated stools which do not become semifluid after the administration of succinylsulfathiazole show only a partial lowering of the number of susceptible organisms.

4. On incubation at 37 C., the coliform organisms may multiply rapidly in some specimens of feces intimately mixed with succinylsulfathiazole.

5. The presence of extensive ulcerative lesions of the intestinal tract retards the rate at which the coliform organisms disappear under therapy, and the final level of the coliform population probably remains somewhat higher than in those instances in which the mucosa of the bowel is intact.

In the attempt to explain these rather diverse conditions which are unfavorable to the action of the drug, one might infer that an accumulation of paraaminobenzoic acid or a like substance in the feces reacts with substance X in these adverse circumstances and forms a metabolite suitable for normal metabolic processes of certain bacteria. Watery diarrhea due to irritation of the mucous membrane and the presence of extensive ulcerative lesions of the intestinal tract furnish a poor absorbing surface, and probably in these conditions additional inhibiting substances pour out. Hard, inspissated fecal material, as well as feces admixed and coated with liquid petrolatum, provides a poor surface for intimate contact with the absorbing mucous membrane of the bowel. Those stool specimens which favor the accumulation of inhibitors will allow bacterial proliferation in the presence of active drugs. It is freely admitted that this discussion is entirely speculative since we know of no facts to support or disprove this hypothesis.

As specifically applied to succinylsulfathiazole, these speculations must include a further consideration. Succinylsulfathiazole, as shown by Dr. W. Barry Wood, has practically no in vitro activity. It is therefore likely that succinylsulfathiazole must itself be converted to a more active compound, probably sulfathiazole. The addition of the succinyl radical to sulfathiazole renders it poorly absorbable from the bowel. The free carboxyl group gives succinylsulfathiazole relatively strong acid properties and by salt formation maintains a high ionic concentration of the drug admixed with the intestinal contents. Succinylsulfathiazole, therefore, may be strongly absorbed or adsorbed by the bacterial cells and may be hydrolyzed to give a high local concentration of a reactive, excited form of nascent sulfathiazole in intimate contact with the organism.

It has been observed that freshly voided feces contain only relatively small amounts of sulfathiazole but that after they stand at 37 C., the succinylsulfathiazole is slowly and progressively hydrolyzed to give free sulfathiazole (table 2). Although the amount of free sulfathiazole present in freshly voided feces is small as compared to the amount of succinylsulfathiazole, the concentration of the free sulfathiazole may vary ordinarily from 50 to 200 mg. per hundred cubic centimeters. Such concentrations of sulfathiazole should be sufficient to have strong bacteriostatic activity without any special assumptions as to the excited state of the sulfathiazole molecule.

METHOD OF INVESTIGATION

Each case was studied exhaustively for hemocytologic changes, for accumulation of the drugs in the blood, for the total urinary excretion

TABLE 2.—*Hydrolysis of Succinylsulfathiazole in Feces and in the Aqueous Solution of the Sodium Salt* *

	Molecular Concentration and Ratio of Sulfathiazole and Succinylsulfathiazole					
	In Incubated Stool Specimen			In Incubated Solution of Sodium Salt of Succinylsulfathiazole		
Days in Incubator at 37 C.	Free (mM per L.)	Conjugated (mM per L.)	Ratio: Conjugated-Free	Free (mM per L.)	Conjugated (mM per L.)	Ratio: Conjugated-Free
0	2.55	65.2	25.6	34.6	550	15.9
4	8.05	59.1	7.4	30.7	510	16.6
13	9.8	54.9	5.6	34.8	635	18.2
34	13.3	40.4	3.0	40.35	624	15.2
41	16.5	40.0	2.4	46.4	660	14.2
48	16.85	50.0	2.9	39.6	663	16.7
63	16.5	55.0	3.3	34.4	507	14.7

* Within the rather wide limits of the accuracy of the analytic procedure a freshly expelled stool specimen contains only relatively small quantities of sulfathiazole. At 37 C. succinylsulfathiazole in contact with fecal material undergoes hydrolysis. This may be due to action of bacteria or ferments. The aqueous solution of succinylsulfathiazole sodium is relatively stable.

of the drug and for alterations of the intestinal flora as indicated by quantitative determinations of the coliform bacteria.

Since succinylsulfathiazole is partially hydrolyzed in the bowel and by the tissue cells, the blood will contain sulfathiazole, acetylsulfathiazole and succinylsulfathiazole.

A detailed description of the methods used in this study is given in our other article in this issue.[1b]

PREOPERATIVE PREPARATION

Patients requiring surgical procedures on the intestinal tract receive a low residue diet, no liquid petrolatum and a minimum of cathartics and enemas. As previously stated, watery diarrhea retards the action of succinylsulfathiazole and must be avoided.

An initial oral dose of 0.25 Gm. of succinylsulfathiazole per kilogram of body weight is followed by a maintenance dose of 0.25 Gm. per kilogram daily, divided into six equal portions and given at four hour intervals. Since the bacterial count in the bowel mounts rapidly immediately on withdrawal of the drug, cleansing enemas should not be administered during the forty-eight hour period preceding operation.

The drug must be brought into direct contact with all portions of the bowel to effect an alteration of the bacterial flora. In the presence of enterostomies diverting the fecal stream or excluding various segments of bowel, the drug must be introduced directly into such segments by the most appropriate means.

All urine is saved for analysis. All stools are examined for consistency and odor, and daily bacteriologic counts are made. The coliform bacteria will usually fall from 10,000,000 to less than 1,000 organisms per gram of wet stool in one to seven days. Usually a satisfactory drop is obtained in three to five days. By this time the bowel will have become empty and the feces relatively odorless, and the patient will have been properly prepared for surgical procedures on the large intestine.

THE BOWEL AT OPERATION

When the abdomen of a patient who has been prepared with succinylsulfathiazole is opened, the bowel is found to be collapsed. The intestinal tract is free from gas and fecal material. The mucosa shows no evidence of local irritation due to action of the drug. If necessary, operation can be performed on the open colon without undue fear of peritonitis or local abscess formation.

The protection which is conferred by the action of this drug is illustrated by the following experimental observation. If at laparotomy the bowel of a dog which has received satisfactory succinylsulfathiazole therapy is found to be empty, the descending colon can be divided transversely through one third of its diameter and the abdomen closed with the lesion ordinarily healing without the production of fatal peritonitis.

POSTOPERATIVE ADMINISTRATION OF SUCCINYLSULFATHIAZOLE

Administration of succinylsulfathiazole, in amounts equal to the preoperative dose, is resumed after operation as soon as the patient can take an ounce (28 Gm.) of warm water without undue nausea. Although the patient may be required to take six large (0.5 Gm.) tablets of drug every four hours, it is surprising that nausea and vomiting seldom occur.

The postoperative course is smooth. There is little distention, and gas pains are strikingly diminished. Occasional superficial wound infection has occurred after extensive operations on the large bowel, but deep abscesses and peritonitis have not been encountered.

TABLE 3.—*Dosage of Succinylsulfathiazole with the Concentration of the Drug in the Blood and the Feces and the Quantity of the Drug Excreted in the Urine in Cases in Which the Gastrointestinal Tract Exhibited Various Lesions*

Patient and Weight, Kg.	Day	Daily Dose, Gm.; Divided Into Six Equal Doses	Concentration of the Drug in the Blood, Mg. per 100 Cc.		Daily Urinary Output, Gm.		Concentration of the Drug in the Stools, per Cent	Comment
			Free	Conjugated	Free	Conjugated		
M. N. 56	1	28	....	....	0.07	0.07	....	Large ulcerating carcinoma of rectum; B. coli count dropped from 10^9 to 10^3; operation done after only 3 days of treatment with drug; postoperative course uneventful; no distention, nausea or vomiting; no toxic symptoms; 8.2% of ingested drug excreted in urine
	2	28	1.3	5.6	0.34	0.40	7.5	
	3	14	0.8	1.2	0.33	0.58	5.1	
	4	..	0.84	1.0				
	5	14	1.17	1.2	0.50	0.49		
	6	14	1.30	1.0	0.47	0.76		
	7	14	1.30	1.0	0.37	0.82		
	8	9	1.30	1.2	0.41	0.97	8.0	
	9	..	....	....	0.22	0.62	6.0	
	10	..	....	....	0.13	0.45		
	11	..	....	....	0.06	0.15		
	12	..	....	....	0.06	0.18		
P. R. 70	1	24	....	....	0.24	0.25	....	Ulcerating carcinoma of rectum; coliform organisms dropped from 10^9 to 10^3 in 4 days and remained at this level; operation on ninth day; no postoperative complications; no distention; no gas pains after abdominal perineal resection; no toxic manifestations; 6.85% of ingested drug excreted in urine
	2	18	1.08	2.50	0.47	1.57		
	3	18	1.50	4.70	0.30	0.70		
	4	18	0.80	0.80	0.23	0.46	5.7	
	5	18	1.30	0.20	0.24	0.42	4.8	
	6	18	0.80	3.4	0.54	1.00	4.6	
	7	18	1.00	3.00	0.20	0.40	4.9	
	8	18	1.30	0.80	0.35	0.35	10.5	
	9	12	1.30	2.30	0.04	0.04		
	10	6	1.20	0.00	0.35	0.22		
	11	18	0.80	1.20	0.78	0.34		
	12	6	0.80	2.80	0.60	0.02	3.5	
	13	..	0.75	0.10	0.50	0.57	4.5	
	14	..	1.00	0.33	0.02	0.00		
	15	..	1.2	0.60	0.03	0.00		
	16	..	0.20	0.00	0.00	0.00		
M. E. 75	1	25	....	....	....	....	....	Partial obstruction in sigmoid on basis of old diverticulitis; drug given 5 days before operation; bowel wall much thickened and scarred with numerous small sinuses and diverticula; few small sessile polypi present; some soiling at time of operation; postoperative course uncomplicated—no distention or gas pains; B. coli count dropped from 10^6 to 60 organisms per Gm. of wet stool; although previously there had been a drug reaction with a rash after sulfathiazole therapy, there were no toxic manifestations due to administration of succinylsulfathiazole; 5.8% of ingested drug excreted in urine
	2	18	1.0	1.5	0.28	1.0		
	3	18	0.8	1.4	0.14	1.24		
	4	18	0.5	1.4	0.70	0.28	6.9	
	5	15	1.8	....	0.67	0.00		
	6	0	1.2	3.3	0.21	0.23	8.0	
	7	15	....	....	0.13	0.02		
	8	18	1.0	1.2	0.47	0.82		
	9	18	1.2	1.6	0.24	0.15		
	10	18	0.8	1.7	0.46	1.18		
	11	18	1.3	1.8	0.34	0.24		
	12	18	....	....	0.27	0.27		
	13	18	1.3	2.5	0.43	0.66	5.7	
	14	18	....	....	0.26	0.50		
	15	18	0.7	2.2	0.27	0.61		
	16	18	....	....	0.60	1.33	5.2	
	17	..	....	....	0.26	0.64		
	18	..	0.8	1.7	0.10	0.26	4.4	
	19	..	....	....	0.10	0.23	1.2	
	20	..	0.1	0.4	0	0.10		
B. D. 55	1	30	....	....	....	....	....	Operation several months previously for abscess resulting from perforation of descending colon by fish bone; fecal fistula resulted; actinomycosis found on one examination; attempt made to close fistula without success; sulfathiazole therapy did not prevent extensive breakdown of wound resulting in formation of double-barreled colostomy; 3 mo. later succinylsulfathiazole given (0.25 Gm. per Kg. by mouth and 0.25 Gm. per Kg. in distal limb of colostomy daily); because of involvement of soft tissues sulfathiazole was given beginning on 9th day to saturate general body tissues; colostomy closed on 13th day; sulfathiazole discontinued on 26th day; after operation 0.25 Gm. per Kg. daily of succinylsulfathiazole given by mouth; postoperative course uneventful; no toxic manifestations; coliform count dropped from 10^6 to 0
	2	27	0.6	1.4	0.19	0.36	4.2	
	3	27	0.7	1.5	0.14	0.22	6.5	
	4	27	....	....	0.27	0.28	8.1	
	5	27	1.3	1.6	0.09	0.20		
	6	27	0.8	1.4	0.10	0.22		
	7	27	0.4	1.0	0.28	0.28	8.3	
	8	27	0.3	2.2	0.40	0.01	6.6	
	9	27	1.8	2.3	0.16	0.10	4.2	
	10	27	1.4	....	....	....	5.5	
	11	27						
	12	22.5	5.3	0.8	....	....	1.6	
	13	0	2.4	4.4	....	....	4.9	
	14	11						
	15	13.5	7.2	1.2				
	16	13.5	....	....	....	....	1.4	
	17	13.5	5.4	2.4	....	....	3.4	
	18	13.5						
	19	13.5	4.0	....	....	....	4.8	
	20	13.5	....	....	....	....	5.4	
	21	13.5	....	....	....	....	5.3	
	22	13.5	4.4	1.7				
	23	13.5						
	24	13.5	4.9	0.8				
	25	13.5						
	26	13.5	5.9	0.4				
	27	13.5						
	28	13.5	0.9	1.0				
	29	13.5						
	30	13.5						
	31	13.5						

TABLE 3.—*Continued*

Patient and Weight, Kg.	Day	Daily Dose, Gm.; Divided Into Six Equal Doses	Concentration of the Drug in the Blood, Mg. per 100 Cc.		Daily Urinary Output, Gm.		Concentration of the Drug in the Stools, per Cent	Comment
			Free	Conjugated	Free	Conjugated		
L. N. 27	1	13.7	0.9	1.5	0.28	0.30	....	Boy 10 yr. old with kidney stone, ileostomy and extensive prolapse of ileostomy; operative treatment shown in fig. 1*D*; coliform organisms dropped from 10^{10} to less than 10; uneventful postoperative course; no toxic drug reaction; 6% of ingested drug excreted in urine
	2	7.5	....	....	0.07	0.01		
	3	7.5	0.7	0.8	0.22	0.03		
	4	7.5	....	....	0.20	0.42		
	5	7.5	....	....	0.17	0.02		
	6	7.5	....	....	0.37	0.61		
	7	7.5	1.7	1.0	0.33	0.86		
	8	7.5	....	....	0.27	0.58		
	9	7.5	1.6	1.6	0.10	0.12		
	10	7.5	....	....	0.08	0.25		
	11	7.5	1.4	3.0	0.08	0.26		
	12*	...	....	....	0.09	0.17		
	13	7.5	....	....	0.08	0.14		
	14	7.5	....	....	0.21	0.28		
	15	7.5	....	....	0.38	0.93		
	16	7.5	....	....	0.17	0.31		
	17	7.5	0.9	2.5	0.17	0.41		
	18	7.5	....	....	0.18	0.43		
	19	7.5	....	....	0.16	0.19		
	20	7.5	....	....	0.06	0.04		
	21	7.5	....	....	0.11	0.09		
	22	1.3	0.4	0.2	0.22	0.22		
T. S. 52	1	21	1.4	1.2	0.01	0.24	....	Woman 49 yr. old with rectal bleeding for 2 mo.; polypoid adenocarcinoma of sigmoid; coliform count dropped from 10^{7} to less than 10; open resection of sigmoid with end to end suture; postoperative course uneventful as regards gastrointestinal tract; sustained radial palsy during operation; after operation sulfathiazole given for pulmonary complication; drug reaction with kidney damage; prior to sulfathiazole therapy 3.8% of ingested succinylsulfathiazole excreted in urine; high blood levels from 19th day due to administration of sulfathiazole
	2	13	0.4	1.9	0.17	0.16		
	3	12	....	....	0.31	0.51		
	4	12	1.0	1.4	0.20	0.23		
	5	12	....	....	0.15	0.30		
	6	12	1.1	1.6	0.14	0.16		
	7	12	0.7	0	0.15	0.20		
	8	12	....	....	0.19	0.21		
	9	12	....	....	0.19	0.11		
	10	12	....	....	0.16	0.05		
	11	8	0.9	0.3	0.17	0		
	12	12	0.4	1.6	0.52	0.50		
	13	12	0.5	1.3	0.18	0.23		
	14	12	....	....	0.16	0.03		
	15	12	....	....	0.24	0.24		
	16	12	....	....	0.15	0.30		
	17	12	....	....	0.05	0.07		
	18*							
	19	..	3.5	5.3	1.06	0.45		
	20	12	8.3	2.5	3.95	2.41		
	21	12	....	....	2.90	1.40		
	22	12	5.8	3.6				
	23	12						
	24	12	....	....	2.66	2.05		
	25	12	....	....	1.47	0.93		
	26	12	....	....	1.86	2.07		
	27	12						
	28	12						
	29	12	....	....	1.06	1.64		
	30	6	6.8	1.6	0.74	0.38		
E. A. 72	1	33	....	....	....	....	....	Filipino man 43 yr. old with long history of pain in right lower quadrant of abdomen; exacerbation for past 3 weeks with palpable mass in right lower quadrant of abdomen; operation delayed because of question regarding diagnosis; tumor of cecum found at operation; resection of colon on right side to midtransverse with open ileocolostomy; postoperative course uneventful; dismissed on 17th postoperative day; coliform count dropped to 600; no toxic drug reactions; 4.1% of ingested drug excreted in urine
	2	18						
	3	18						
	4	18	0.86	2.64				
	5	18						
	6	18						
	7	18						
	8	18	0.86	2.83				
	9	18						
	10*	..	....	....	2.19†	1.78†		
	11	5	....	....	0.055	0.058		
	12	15	....	....	0.059	0.043		
	13	15.5	....	....	0.60	0.445		
	14	18	1.29	0.18	0.94	0.62		
	15	18	....	....	0.236	0.416		
	16	18	....	....	0.14	0.23		
	17	18	....	....	0.29	0.40		
	18	18	....	....	0.33	0.35		
	19	18	....	....	0.29	0.42		
	20	18	....	....	0.22	0.35		
	21	18	0.32	2.06	0.27	0.33		
	22	18	....	....	0.29	0.37		

* Day of operation.

† Total preoperative urinary excretion.

TABLE 3.—*Continued*

Patient and Weight, Kg.	Day	Daily Dose, Gm.; Divided Into Six Equal Doses	Concentration of the Drug in the Blood, Mg. per 100 Cc.		Daily Urinary Output, Gm.		Concentration of the Drug in the Stools, per Cent	Comment
			Free	Conjugated	Free	Conjugated		
L. E.	1	24	....	....	....	....	....	Woman 57 yr. old with fecal fistula after resection of cecum for carcinoma 6 years before present admission; coliform count dropped from 10^6 to less than 10; operative procedure shown in fig. 1*C*; superficial wound infection and alpha Str. faecalis cystitis after operation; postoperative course otherwise uneventful; dismissed on 22d day after operation; no toxic reaction to drug; 6.4% of ingested drug excreted in urine
48	2	12	0.86	8.12				
	3	12						
	4	12						
	5	12						
	6	12						
	7	12						
	8	12						
	9	12						
	10	12						
	11	12						
	12*	..	....	....	2.54†	7.15†		
	13	6	....	....	0.16	0.033		
	14	12	1.73	0.72				
	15	12						
	16	12						
	17	12						
	18	12	....	....	0.251	0.366		
	19	12	....	....	0.094	0.122		
	20	12	....	....	0.062	0.076		
	21	12						
	22	12	0.43	1.55	0.128	0.156		
	23	12						
	24	..	....	....	0.064	0.142		
H. S.	1	4	....	....	....	....	....	Negro woman 63 yr. old with severe diarrhea and large amounts of blood in stools; hemoglobin content, 20%; carcinoma of hepatic flexure; repeated transfusions; coliform count did not drop until diarrhea was controlled with lead and opium; count then dropped immediately from 10^6 to 700; resection of colon on right side with ileotransversostomy; postoperative course uncomplicated; no toxic drug reaction; dismissed on 20th postoperative day; 2.4% of ingested drug excreted in urine; hemoglobin content, 80%
45.4	2	12	....	....	0.000	0.025		
	3	12	....	....	0.128	0.354		
	4	12	....	....	0.010	0.023		
	5	12	....	....	0.113	0.272		
	6	12	....	....	0.062	0.176		
	7	12						
	8	15	0.86	2.68	0.035	0.094		
	9	18	....	....	0.092	0.193		
	10	18	....	....	0.036	0.082		
	11	18						
	12	18						
	13	18						
	14	18						
	15	18	....	....	0.039	0.145		
	16	12						
	17*	..	....	....	0.115	0.326		
	18	12						
	19	18	....	....	0.101	0.224		
	20	18						
	21	18	....	....	0.118	0.171		
	22	18	....	....	0.047	0.146		
	23	18	....	....	0.036	0.046		
	24	18	....	....	0.035	0.058		
	25	18	....	....	0.068	0.080		
	26	18	....	....	0.197	0.302		
	27	..	....	....	0.065	0.119		
	28	..	....	....	0.294	0.336		
G. R.	1	15	....	....	0.103	0.231	....	Woman 33 yr. old with multiple fecal fistulas; five previous abdominal operations, including colectomy and ileosigmoidostomy; coliform organisms dropped from 10^7 to 10^3; extensive operation with open end to side anastomosis of bowel in presence of a massive adhesion; course uncomplicated; all fistulas closed; no toxic drug reaction; 3.7% of ingested drug excreted in urine; dismissed on 22d postoperative day
	2	15	....	....	0.255	0.796		
	3	15	0.43	1.42	0.158	0.536		
	4	15	....	....	0.104	0.294		
	5	15	....	....	0.309	0.556		
	6	15	....	....	0.202	0.493		
	7	15						
	8	19	1.08	0.86	0.176	0.300		
	9	27	....	....	0.316	0.845		
	10	27	....	....	0.257	0.655		
	11	27	1.08	2.12	0.306	0.977		
	12	27	....	....	0.212	0.590		
	13	27	....	....	0.202	0.501		
	14	27	....	....	0.426	0.644		
	15	27	....	....	0.145	0.614		
	16*	15	....	....	0.234	0.938		
	17	5	....	....	0.072	0.223		
	18	15	....	....	0.044	0.108		
	19	15	....	....	0.310	0.325		
	20	15	....	....	0.172	0.185		
	21	15	....	....	0.172	1.242		
	22	15	1.38	2.84	0.530	0.596		
	23	15	....	....	0.128	0.255		
	24	15	....	....	0.119	0.180		
	25	15	....	....	0.127	0.133		
	26	15	....	....	0.026	0.026		
	27	15	....	....	0.084	0.023		
	28	15	....	....	0.050	0.113		
	29	..	....	....	0.062	0.041		
	30	..	....	....	0.034	0.082		
	31	..	....	....	0.009	0.026		
	32	..	....	....	0.024	0.000		
	33	..	0.43	0.74				
	34	..	....	....	0.004	0.000		

* Day of operation.
† Total preoperative urinary excretion.

While the action of succinylsulfathiazole is largely restricted to its local effect on the contents of the gastrointestinal tract, other derivatives of sulfanilamide, especially sodium sulfathiazole administered intravenously, are not given except when extra-abdominal complications develop. Patients receiving only succinylsulfathiazole experience an unusually simple convalescence.

In the course of this study no additional derivatives of sulfanilamide have been placed in the peritoneal cavity or in the operative wound, because of the desire to study the effect of succinylsulfathiazole alone. Subsequently, in view of the apparent advantage of placing sulfanilamide or one of its derivatives in the abdominal cavity and the wound at the time of operation, this procedure might well be added to succinylsulfathiazole therapy. Again, it might be desirable in certain instances to saturate the general body tissues with one of the readily absorbed compounds of this group both before and after operation, and this procedure has, in fact, been carried out on 2 of the patients included in this study (table 3).

The period of postoperative therapy is determined by the condition observed at operation. After abdominoperineal resection for carcinoma of the rectosigmoid, the drug is given for approximately one week to allay distention. However, after colonic resection with primary suture, it is administered for twelve to fourteen days.

Again it should be emphasized that the drug should not be withheld after operation if it is at all possible for the patient to take water, because the bacterial flora is rapidly restored on withdrawal of the compound. It is not unusual for the coliform count to increase from 100 to 10,000,000 organisms per gram of wet stool within twenty-four hours after the discontinuance of therapy.

SUCCINYLSULFATHIAZOLE IN TREATMENT

In an attempt to present evidence of the apparent value of an agent which will modify the physical character and the bacterial count of the fecal material in the gastrointestinal tract before and after operations on the bowel, the pertinent data covering a few of the patients operated on and treated with succinylsulfathiazole are given in table 3.

The material presented in tabular form readily indicates the general type of patient treated. A detailed presentation of the case of L. N. (table 3) discloses a particularly interesting problem. A 10 year old boy was operated on for acute intestinal obstruction fourteen months before the hospitalization recorded in the table. Appendectomy had been performed twenty-two months before the appearance of acute obstructive symptoms. One week prior to the present admission roentgen study made after the finding of hematuria revealed a staghorn

stone of the right kidney. On admission, examination showed also a large segment of small bowel prolapsed through a right pararectus tangential enterostomy. Communication between the enterostomy, the colon and the rectum could not be demonstrated.

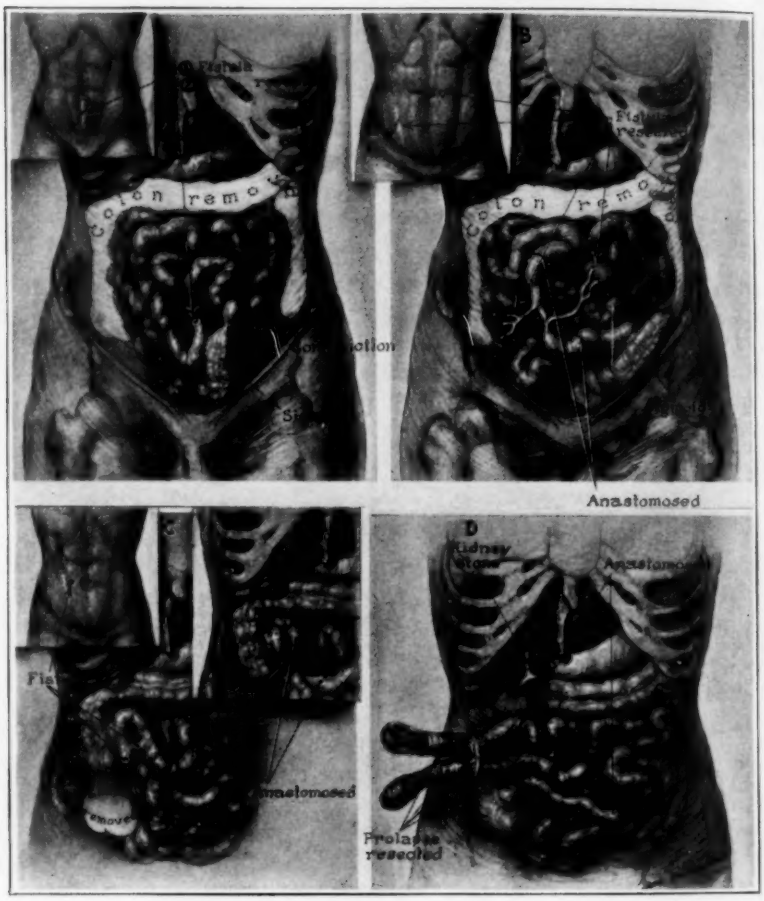

Figure 1

(See legend on opposite page)

Anticipating that operation might necessitate an extensive intra-abdominal procedure, we considered it desirable to lessen the virulence of the intestinal flora. The presence of a kidney stone should preclude any such attempt by the administration of sulfanilylguanidine, because we have shown that kidney stones composed of sulfanilylguanidine are formed in a high percentage of dogs receiving therapeutic doses of that drug. Since, however, Poth, Knotts, Lee and Inui [1b] had demonstrated

that succinylsulfathiazole can be excreted in high concentration in the urine as a soluble salt, it was considered safe to administer succinylsulfathiazole in the presence of a stone in the kidney. The drug was given without evidence of any change in the urinary tract, and satisfactory surgical treatment was undertaken as indicated in figure 1 *D*.

EXPLANATION OF FIGURE 1

Pathologic conditions of the bowel presenting various problems in the administration of succinylsulfathiazole.

A. A fecal fistula developed after colectomy and ileosigmoidostomy for ulcerative colitis. The patient had received sulfanilylguanidine prior to operation; he returned to the hospital for closure of the fistula. Administration of succinylsulfathiazole failed to lower coliform organisms below 30,000 colonies per gram of wet stool. At operation a short constricted blind end of sigmoid was found to contain 1,000,000 B. coli per gram of fecal material. A culture from the proximal loop showed approximately 1,000 B. coli per gram of bowel contents. The drug was not entering the short blind end of sigmoid in sufficient quantity. Closure was effected with primary healing.

B. This patient had five surface fecal fistulas after five operations during the course of which colectomy was performed for chronic ulcerative colitis. No feces were passed per rectum. The patient received 0.25 Gm. of succinylsulfathiazole per kilogram daily in six oral doses and an equal amount of the drug per rectum administered in three daily instillations. Culture of the material obtained from both the fistulas and the rectum showed less than 1,000 B. coli per gram. At operation a maze of adhesions was encountered. In dissecting out the fistulas, two openings were made in the bowel. The maze of adhesions was unraveled by opening the blind stump of the sigmoid, introducing catheters into the three open ends of bowel and placing a fourth catheter into the rectum to demonstrate the course and continuity of the bowel. These catheters were handled without regard to the fact that they had been in contact with fecal material. Primary end to end suture was performed, the wound was closed with silk, and healing occurred by primary intention.

C. A fecal fistula occurred after resection of a carcinoma of the cecum six years previously. Feces were seldom passed per rectum. Succinylsulfathiazole was administered orally and per rectum in doses of 0.25 Gm. per kilogram daily by each route. After a satisfactory alteration of the intestinal flora, dissection of the fistulas, resection of a segment of bowel and end to end suture were done as indicated. The result was healing by primary intention.

D. A boy of 10 years entered the hospital in the condition shown. In the presence of a kidney stone, succinylsulfathiazole was given by mouth and introduced into the distal limb of the enterostomy. Obviously, the drug could not possibly be introduced into the distal atrophic blind segment of the ileum. Material from the proximal limb of the ileostomy contained less than 10 B. coli per gram. End to side anastomosis was performed as indicated. The postoperative course was distinguished by the occurrence of only moderate distention and transient gas pains. Damage resulting to the urinary tract from the growth of the kidney stone by the crystallization of the drug on the surface was not evident.

TOXIC MANIFESTATIONS

The administration of succinylsulfathiazole to patients with various lesions of the gastrointestinal tract presents no special problems. The degree of absorption is essentially the same and is not conditioned by the state of the bowel. The drug has been administered in the presence of partial obstruction without evident increase in the quantity of drug excreted in the urine. A series of patients from whom complete urinary collections were obtained for the entire period of therapy showed an average excretion by the kidneys of 4.85 per cent of the ingested compound. The concentration of the drug in the blood usually ranged from 0.5 to 1.0 mg. per hundred cubic centimeters for sulfathiazole and from 1.0 to 2.0 mg. for the conjugated sulfathiazoles. Toxicity is conditioned

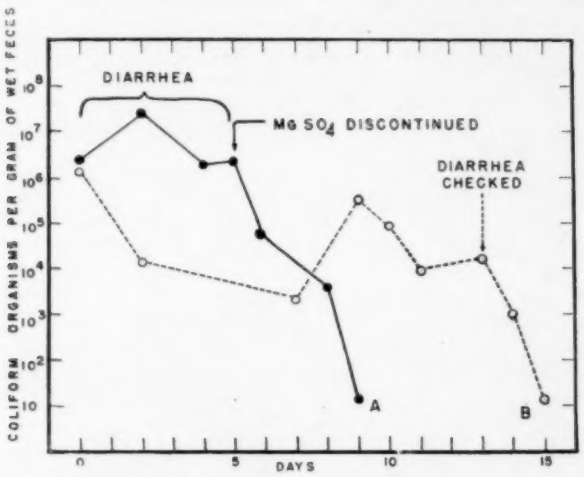

Fig. 2.—Retardation of the action of succinylsulfathiazole in the presence of watery diarrhea.

A. The patient received 0.25 Gm. per kilogram daily of succinylsulfathiazole divided into six equal doses for nine days. During the first five days this patient had watery diarrhea due to the administration of magnesium sulfate. The count of coliform organisms remained unchanged during this period. After discontinuance of administration of magnesium sulfate on the fifth day, the diarrhea stopped, and the intestinal flora was profoundly altered.

B. This patient had a large ulcerating lesion, diagnosed as carcinoma, at the hepatic flexure of the colon, accompanied by severe protracted hemorrhage and diarrhea. Succinylsulfathiazole (0.5 Gm. per kilogram daily) failed to alter satisfactorily the intestinal flora until the diarrhea was checked by the administration of lead and opium in the form of pills.

not merely by the concentration of a drug in the blood but also by the total quantity of the drug absorbed and disposed of by the body tissues. There were no hemocytologic changes.

Vomiting did not occur. Some patients complained of a loss of appetite, while others said that the appetite was improved. Three

patients had diarrhea. One of these patients had a massive hemorrhage from a large eroded carcinoma of the rectum. No rashes occurred. In patients with a rash from sulfathiazole this toxic manifestation did not again develop on the administration of succinylsulfathiazole, even though the sulfathiazole rash disappeared only a day before succinylsulfathiazole therapy was started. If, however, succinylsulfathiazole was given while the rash due to sulfathiazole was still present, clearing apparently did not occur. In summary, it can be stated that severe toxic manifestations due to the administration of succinylsulfathiazole were not observed. The drug was given continuously for periods of sixteen weeks without untoward effects.

FAILURES

Severe watery diarrhea, whatever the cause, is the most frequent cause of failure to lower the bacterial flora. Obviously, the remedy is to check the diarrhea (fig. 2). If the diarrhea cannot be stopped, it may not be possible to effect a significant alteration of the intestinal bacterial flora even with massive doses of succinylsulfathiazole.

In the presence of a blind loop of bowel the drug may not enter the segment in sufficient quantity for antibacterial effect. An attempt should be made by change of position to cause the drug to enter the isolated segment; otherwise a favorable result cannot be expected (fig. 1 *A*).

COMMENT

An intensive study of the first 100 patients to whom succinylsulfathiazole has been administered permits some rather definite impressions to be formed.

Certain conditions interfere with the action of the drug. If these can be eliminated, adequate administration of the compound always results in profound alteration of the physical properties and the bacterial flora of human feces. In 5 of the 100 cases included in this study satisfactory lowering of the coliform count was not realized; in 2 of these 5 cases there was severe, uncontrollable diarrhea; in 2 cases there were blind loops of bowel into which the drug did not enter, and in the fifth case there was intestinal indigestion so that the stools did not become semifluid during drug therapy. An occasional failure to alter the stools will no doubt occur, but success can be anticipated for about 95 per cent of all patients adequately treated.

In the bacteriologic investigation only the coliform organisms were studied quantitatively. B. coli was selected for quantitative study because of the ease with which its differentiation is possible on desoxycholate agar plates inoculated with such complicated bacterial mixtures as are present in feces. Because of the profound changes in the feces, it is likely that various organisms, including the amaerobic bacteria, are

affected. The shift in the count of B. coli may well be considered a convenient indicator.

While it is not desirable to draw hard and fast conclusions from such a limited clinical study, one is impressed by the smooth convalescence experienced by patients receiving preoperative and postoperative treatment with succinylsulfathiazole. Further, we present these observations and impressions with the full realization that much more experience must be gained before dogmatic statements can be made regarding the effectiveness of succinylsulfathiazole as an aid to surgical procedures. If after a minimum of five years of critical use this drug, or another of similar properties has earned a place in the surgical armamentarium, the impressions and speculations presented here will have proved validity. The smooth, uncomplicated postoperative convalescence appears significant even at this time, and one is inclined to feel that some such regimen will prove to be an adjuvant to surgical procedures on the large bowel. It is not intended to imply that this is a signal to permit poor surgical performance or to relax rigid surgical asepsis. Rather it is hoped that a procedure of this kind may add another safeguard. Patients receiving succinylsulfathiazole should be closely observed with frequent determinations of the concentration of the compound in the blood and of the total urinary output of the drug.

One postoperative death has occurred. In this instance anuria developed after a Miles operation for carcinoma of the rectum. Postmortem examination showed that both ureters had been mechanically blocked by a large pack placed in the posterior wound of an abdominal perineal resection.

SUMMARY

Succinylsulfathiazole has been administered to 100 human beings.

Approximately 5 per cent of the succinylsulfathiazole administered orally in therapeutic dosage levels was excreted in the urine. A detailed report of the urinary excretion of the drug is given.

Succinylsulfathiazole can be maintained in high concentration in the diseased gastrointestinal tract of man with low concentrations of the drug in the blood and without the development of toxic manifestations.

A profound change in the physical characteristics and the bacterial flora of the feces can be expected in 95 per cent of all cases after adequate treatment with succinylsulfathiazole.

The possible mechanism of action of succinylsulfathiazole is discussed.

Observations on a series of patients treated with succinylsulfathiazole and operated on are reported.

Drs. Warfield M. Firor, Alfred Blalock, James M. Mason III and numerous other physicians and surgeons gave us help and allowed us to use their patients in this study.

SODIUM SULFADIAZINE IN THE TREATMENT OF EXPERIMENTAL STREPTOCOCCIC INFECTION

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AND
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The purpose of this study is to determine the effect of large doses of sodium sulfadiazine (the monohydrate sodium salt of 2-[paraamino-benzenesulfonamido]-pyrimidine) given subcutaneously to rabbits with wounds inoculated with a measured amount of a culture of beta hemolytic streptococcus of known virulence.

METHOD

Rabbits weighing from 2,200 to 3,800 Gm. were used. Soluble pentobarbital (0.80 cc. of a solution containing 0.06 Gm. of pentobarbital per cubic centimeter) administered in an aural vein supplemented by light open drop ether was used to induce anesthesia for all operations. Aseptic technic was used throughout. A longitudinal incision 2 cm. long was made 1 cm. to the left of the midline posteriorly and 2 cm. inferior to the lowest rib. The skin, the subcutaneous tissue and the muscle sheath were incised. By means of a brass cork borer with a diameter of 1 cm., a segment of sacrospinalis muscle 2 cm. in depth was removed. The muscle was crushed with an artery forceps and replaced. The fascia was closed with interrupted sutures of fine silk and the skin with a continuous suture of fine silk. An identical procedure was performed on the right side except that a pledget of dry cotton 1 cm. square and approximately 2 mm. thick was placed in the wound before the muscle was inserted. A two layer thickness of gauze was placed over each incision; this was sealed with collodion.

EXPERIMENTS

Control Group 1 (Operation).—Two animals were operated on with the procedure just outlined. All four wounds healed by first intention. The animals were observed for two weeks after operation.

Control Group 2 (Inoculation).—Twelve animals were operated on in the manner described. A stock broth culture of beta hemolytic streptococcus was obtained from Dr. D. Murray Angevine.[1] This strain was termed by him NY 5.

From the Department of Surgery, New York Hospital and Cornell University Medical College.

1. Cecil, R. L.; Angevine, D. M., and Rothbard, S.: Experimental Arthritis in Rabbits Produced with Streptococci and Other Organisms, Am. J. M. Sc. **198**: 463-475, 1939.

It was originally isolated in a case of scarlet fever by Dr. Alphonse R. Dochez. Its virulence for rabbits was known. The culture used was eighteen hours old and contained 107,000,000 organisms per cubic centimeter; 0.10 cc. was implanted

TABLE 1.—*Blood Levels of Sodium Sulfadiazine Administered to Two Rabbits*

Rabbit 4		Rabbit 64	
Time	Sodium Sulfadiazine, Mg. per 100 Cc.	Time	Sodium Sulfadiazine, Mg. per 100 Cc.
10 a.m.	1.2	10 a.m.	2.8
11 a.m.	Trace	11 a.m.	1.8
2 p.m.	1.5	2 p.m.	3.8
4 p.m.	1.5	4 p.m.	1.2
8 p.m.	0.92	8 p.m.	2.1
12 midnigh	Faint trace	12 midnight	Very faint trace
8 a.m.	Very faint trace	8 a.m.	Very faint trace

TABLE 2.—*Data on Duration of Life and Cultures of Rabbits in Control Group 2*

Rabbit	Duration of Life, Hr.	Blood Culture	Culture of Wound in Right Lumbar Region	Culture of Wound in Left Lumbar Region
46	26	Beta hemolytic streptococcus	Beta hemolytic streptococcus	Beta hemolytic streptococcus
69	16	Beta hemolytic streptococcus	Beta hemolytic streptococcus	Beta hemolytic streptococcus
70	16	Beta hemolytic streptococcus, Staphylococcus albus, gram-negative bacilli	Beta hemolytic streptococcus	Beta hemolytic streptococcus
73	16	Beta hemolytic streptococcus	Beta hemolytic streptococcus, gram-negative bacilli	Beta hemolytic streptococcus, gram-negative bacilli
76	20	Beta hemolytic streptococcus	Beta hemolytic streptococcus	Beta hemolytic streptococcus
77	23	Beta hemolytic streptococcus	Beta hemolytic streptococcus	Beta hemolytic streptococcus
80	16	Beta hemolytic streptococcus	Beta hemolytic streptococcus	Beta hemolytic streptococcus
81	80	Beta hemolytic streptococcus	Beta hemolytic streptococcus	Beta hemolytic streptococcus
83	Survived	No growth	Beta hemolytic streptococcus	Beta hemolytic streptococcus
84	18	Beta hemolytic streptococcus	Beta hemolytic streptococcus	Beta hemolytic streptococcus
88	18	Beta hemolytic streptococcus	Beta hemolytic streptococcus	Beta hemolytic streptococcus
91	108	Beta hemolytic streptococcus	Beta hemolytic streptococcus	Beta hemolytic streptococcus

into each incision before the muscle or the cotton was inserted. Except for the absence of the determination of sodium sulfadiazine in the blood, these animals were followed exactly in the manner to be described under "Crucial Experiment."

Control Group 3 (Administration of Sodium Sulfadiazine).—A 10 per cent solution of sodium sulfadiazine in distilled water was used. In the New York Hospital 0.10 Gm. per kilogram of body weight is used clinically as the daily dose; this amount was administered in three divided doses at 8 a. m., 12 noon and 4 p. m. to 2 rabbits. Blood was obtained at 10 a. m., 11 a. m., 2 p. m., 4 p. m., 8 p. m., 12 midnight and 8 a. m. The level of sodium sulfadiazine in the blood is shown in table 1.

As can be noted, this dosage failed to produce a satisfactory blood level. Hence, a total daily dose of 0.4 Gm. per kilogram of body weight was arbitrarily used. This was given in six divided doses at four hour intervals. The drug was administered subcutaneously in the costovertebral region several centimeters cephalad to the incision. The drug was given to 6 animals for seven days. Blood

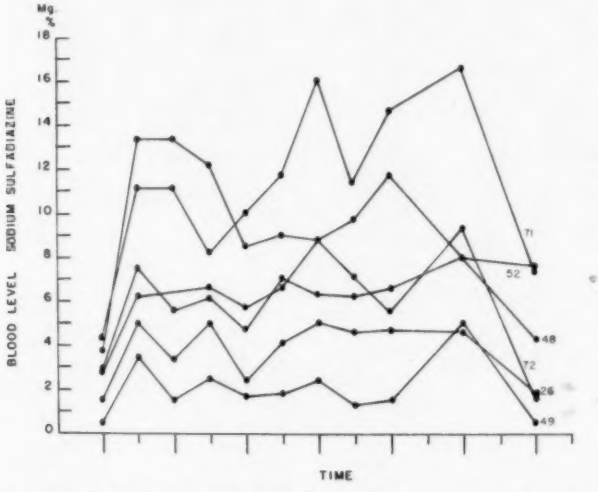

Chart 1.—Blood levels of sodium sulfadiazine for rabbits in control group 3. Time is indicated in twelve hour intervals.

was removed from an incised aural vein at twelve hour intervals for the first four days and twenty-four hour intervals for the last three days. No untoward reactions, either local or systemic, were noted in these animals, and all survived. The blood levels are shown in chart 1.

Clinical Experiment.—The crucial experiment was done on two series of 12 animals each. Twenty-four rabbits were operated on as described; 0.10 cc. of the previously mentioned culture was implanted into each wound. At 8 o'clock on the morning of operation, ⅙ of the total daily dose (0.4 Gm. per kilogram) was administered. All the animals were operated on between 9 a. m. and 12 noon. The time at which the operation was completed was recorded. The drug was administered every four hours as described. Blood was withdrawn at the stated intervals for determination of the level of sodium sulfadiazine in the blood. When death occurred,

TABLE 3.—*Data on Duration of Life and Cultures of Rabbits Used in Crucial Experiment*

Rabbit	Duration of Life, Hr.	Blood Culture	Culture of Wound in Right Lumbar Region	Culture of Wound in Left Lumbar Region
		A. Series 1.		
57	Survived	No growth	No exudate	No exudate
58	26	Beta hemolytic streptococcus	Beta hemolytic streptococcus	Beta hemolytic streptococcus
59	24	Beta hemolytic streptococcus, gram-negative bacilli	Beta hemolytic streptococcus, gram-negative bacilli	Beta hemolytic streptococcus, gram-negative bacilli
66	18	No growth	Beta hemolytic streptococcus	Beta hemolytic streptococcus, gram-negative bacilli
67	120	No growth	Beta hemolytic streptococcus	Beta hemolytic streptococcus
68	14	Beta hemolytic streptococcus	Beta hemolytic streptococcus	Beta hemolytic streptococcus
78	42	Gram-negative bacilli	Beta hemolytic streptococcus	Beta hemolytic streptococcus
79	14	No growth	Beta hemolytic streptococcus	Beta hemolytic streptococcus
85	Survived	No growth	Beta hemolytic streptococcus	Beta hemolytic streptococcus
86	18	Beta hemolytic streptococcus	Beta hemolytic streptococcus	Beta hemolytic streptococcus
89	48	No growth	Beta hemolytic streptococcus	Beta hemolytic streptococcus
90	Survived	No growth	No exudate	No exudate
		B. Series 2.		
5	Survived	No growth	Staph. albus	Beta hemolytic streptococcus, Staph. albus, Staph. aureus
11	49	Staph. albus	Beta hemolytic streptococcus	Beta hemolytic streptococcus
28	61	Bacillus subtilis	Beta hemolytic streptococcus	Beta hemolytic streptococcus
31	52	No growth	Beta hemolytic streptococcus	Beta hemolytic streptococcus
32	Survived	No growth	Beta hemolytic streptococcus, Staph. albus	Staph. aureus, Staph. albus, gram-positive bacilli, gram-negative bacilli
36	32	No beta hemolytic streptococcus, Staph. aureus	Beta hemolytic streptococcus, gram-negative bacilli	Beta hemolytic streptococcus
43	66	No beta hemolytic streptococcus, B. subtilis	Beta hemolytic streptococcus	Beta hemolytic streptococcus
45	74	No beta hemolytic streptococcus, Staph. aureus	Beta hemolytic streptococcus	Beta hemolytic streptococcus
47	37	No beta hemolytic streptococcus, B. subtilis	Beta hemolytic streptococcus	Beta hemolytic streptococcus
64	24	Beta hemolytic streptococcus, Staph. albus, Staph. aureus	Beta hemolytic streptococcus	Beta hemolytic streptococcus
74	18	No beta hemolytic streptococcus, diphtheroid bacilli	Beta hemolytic streptococcus	Beta hemolytic streptococcus
92	22	No beta hemolytic streptococcus, Staph. albus	Beta hemolytic streptococcus	Beta hemolytic streptococcus

the time of death was noted. The 19 animals which died were submitted to autopsy, the thoracic cavity was opened, and heart blood removed for culture. The wounds were inspected and opened, and cultures were taken under aseptic precautions. There was no actual cellulitis or evidence of spreading infection in any case. When the skin sutures were removed, it was found that in a few instances the crushed muscle segment had become extruded from beneath the fascia. The muscle segment in most of the wounds showed beginning gross

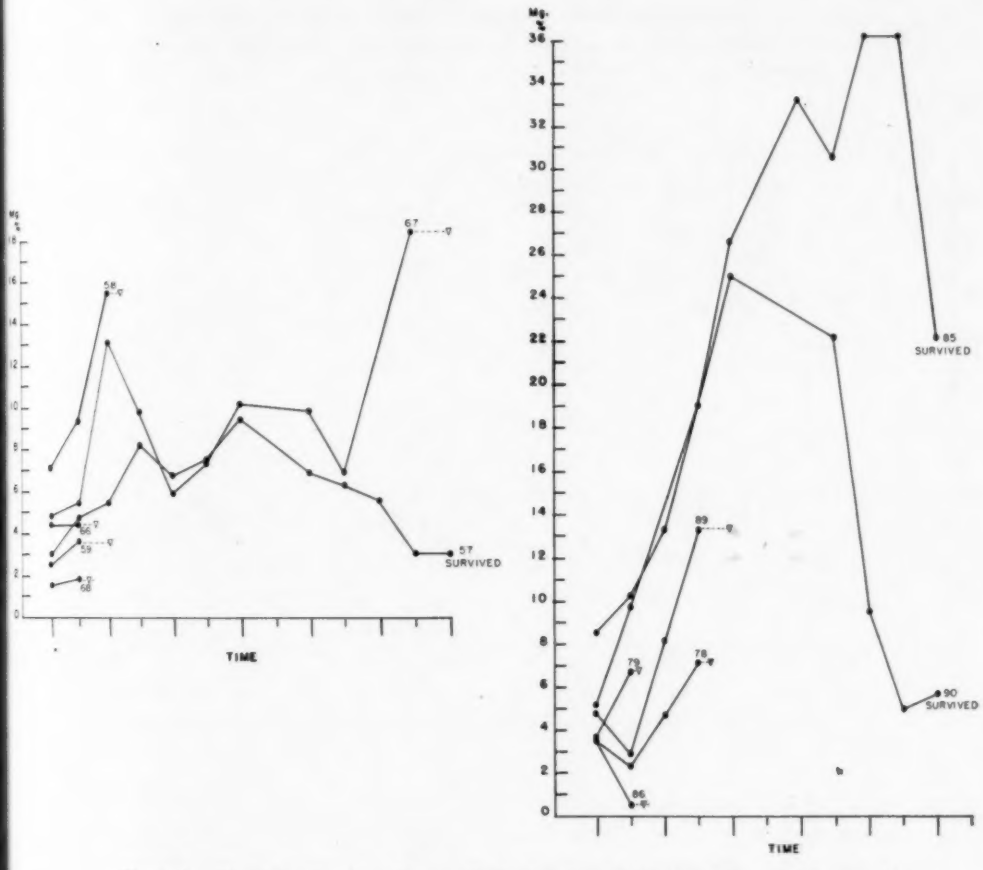

Chart 2.—Blood levels of sodium sulfadiazine for rabbits used in crucial experiment, series 1. In this and the following chart the levels are charted in groups of 6 for convenience in reading. Time is indicated in twelve hour intervals; the broken lines with triangles signify that the rabbit died.

autolysis. In all cases the depth of the cavity on the right was found to be practically dry when the cotton was removed, while in all instances the wound on the left contained a minute amount of an odorless exudate. The appearance

of the wounds in the treated animals was not grossly different from that of the wounds in the inoculated control rabbits.

The animals which survived four days were examined as follows: Blood was removed from the aural vein for culture. The dressing of gauze impregnated with collodion was removed from the wounds; the latter were inspected, and an effort was made to evacuate exudate. If this was possible, cultures were made. Thus, the blood from all rabbits was cultured; the material for culture was taken from the ear of 5 rabbits which survived and from the heart of 19 rabbits which died. Cultures were made from the wounds of 3 of the 5 surviving rabbits. From the other 2, no exudate could be obtained. The results of the making of

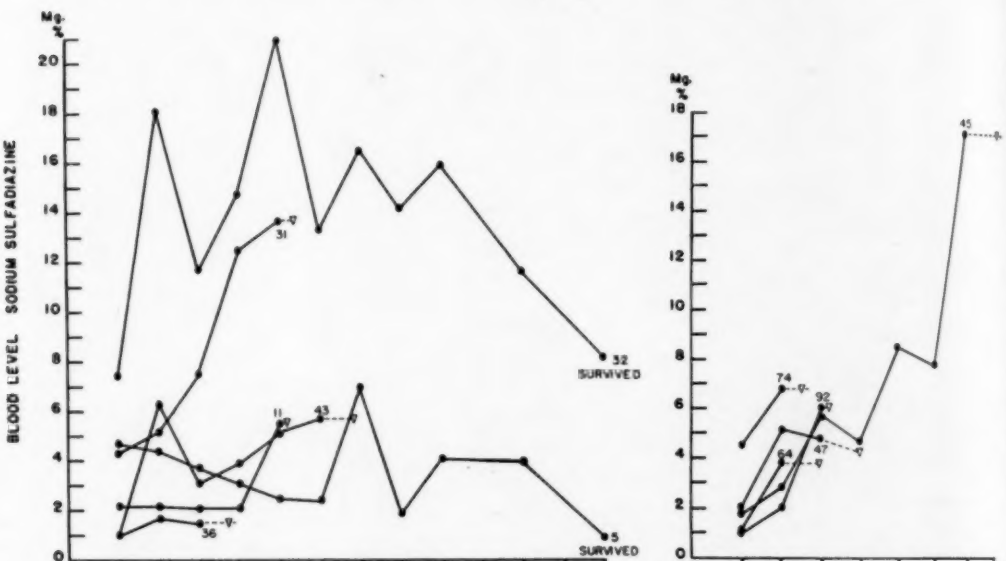

Chart 3.—Blood levels of sodium sulfadiazine for rabbits used in crucial experiment, series 2.

these cultures of the wounds and of blood from the heart or the ear and the length of time of survival are shown in table 3. The data on the inoculated control rabbits are given in table 2.

Charts 2 and 3 show graphically the blood level of sodium sulfadiazine in milligrams per hundred cubic centimeters and the survival period in the crucial experiment.

Summary (see table 4).—Control Group 2 (Inoculation): In examining the cultures of the 12 control rabbits inoculated with a culture of beta hemolytic streptococcus of known virulence, it was found that all blood cultures were positive except 1 and that all wound cultures were positive. The average survival period of 11 of these animals that died was thirty-two hours; 1 animal lived.

Crucial Experiment (series 1): In the first crucial experiment only 4 blood cultures were positive for beta hemolytic streptococcus, while 8 failed to yield a growth of these organisms. All wounds but four (2 rabbits) had an exudate in them which was positive for beta hemolytic streptococcus. The average survival period of 9 of these animals that died was thirty-six hours; 3 animals survived.

Crucial Experiment (series 2): In the second series of the crucial experiment only 1 blood culture was positive for beta hemolytic streptococcus, while 11 failed to show growth. All animals but 1 had wound exudate with beta hemolytic streptococcus. The average survival period of 10 of these animals that died was forty-three and four-tenths hours; 2 animals survived. In all animals except 1 there was an exudate in the wounds from which the beta hemolytic streptococcus was grown.

TABLE 4.—*Data on Death, Positive Blood Cultures and Survival Time of Rabbits in Control Group 2 and Those Used in the Crucial Experiment*

	Rabbits	Died	Positive Blood Cultures	Average Survival Time, Hr.
Control group 2.....	12	11	11	32
Crucial experiment, series 1....	12	9	4	36
Crucial experiment, series 2....	12	10	1	43.4

COMMENT

In these experiments a lethal amount of culture of beta hemolytic streptococcus of known virulence was placed in the wounds of rabbits. The average survival period of 12 control animals was thirty-two hours; all but 1 had positive blood cultures. When sodium sulfadiazine (0.4 Gm. per kilogram of body weight) was given to similar animals at four hour intervals, the survival period of the animals that died was slightly increased; 5 animals (20.8 per cent) lived, and the blood became sterile, although there was no consistent blood level concentration of the drug. The bactericidal action of the drug is evident as far as the blood stream is concerned. The failure of the drug to affect the growth of the organisms in the wounds was not unexpected, and it is probable that the absorption of toxin from the wounds was the cause of death, even though the blood was rendered sterile.

The drug is quickly taken up by the blood stream when given subcutaneously, and it is likewise so rapidly lost from the blood stream that frequent administrations are necessary if the blood stream is to contain a sufficient amount of the drug to be bactericidal. The apparent lack of effect on the bacteria in the wound following the administration of the drug by this method suggests the advisability of placing the drug directly in the wound.

CONCLUSIONS

Sodium sulfadiazine (0.4 Gm. per kilogram of body weight) given subcutaneously to rabbits every four hours did not result in a constant blood level concentration of the drug.

This amount of the drug given in this manner was bactericidal for beta hemolytic streptococcus in the blood.

Sodium sulfadiazine prolonged the survival period of rabbits having wounds inoculated with a known culture of beta hemolytic streptococcus; 5, or 20.8 per cent, of the animals survived in a series of 24.

Sodium sulfadiazine (0.4 Gm. per kilogram of body weight) given subcutaneously did not result in sterilization of the wounds containing devitalized muscle or devitalized muscle plus a foreign body (cotton).

SULFADIAZINE IN EXPERIMENTAL STREPTOCOCCIC INFECTION

A STUDY OF THE EFFECTS OF LOCAL IMPLANTATION

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In another paper [1] we report the results obtained by the subcutaneous administration of sulfadiazine sodium (the monohydrate sodium salt of 2-sulfanilamidopyrimidine) to rabbits with wounds inoculated with a measured amount of culture of beta Streptococcus haemolyticus of known virulence. This study represents the results of the implantation of sulfadiazine (2-sulfanilamidopyrimidine) into similar wounds at the time of operation.

METHOD

The method was the same as that previously described. Rabbits weighing 2,200 to 3,800 Gm. were used. With the animal under anesthesia induced by intravenous administration of pentobarbital sodium supplemented by light open drop ether inhalation and by means of aseptic technic, a longitudinal incision of 2 cm. was made posteriorly 1 cm. to the left of the midline and 2 cm. caudad to the lowest rib. The incision was carried down to the sacrospinalis muscle, and with a brass cork borer 1 cm. in diameter, a segment of this muscle 2 cm. in depth was removed. An eighteen hour old broth culture of the NY 5 strain of the beta hemolytic streptococcus, a culture containing 100,000,000 organisms per cubic centimeter, was used; 0.1 cc. of this culture was placed in the wound. The muscle segment was crushed with an artery clamp and replaced, and the wound was closed with silk. An identical procedure was carried out on the right side except that a pledget of dry cotton 1 cm. square and 2 mm. in thickness was placed in the wound before the muscle was reinserted. A gauze dressing impregnated with collodion (4 per cent solution of pyroxylin in a mixture of ethyl oxide and alcohol) was applied. In the control animals only the procedure just outlined was done.

In a group of 6 animals, five minutes, and in a group of 12 animals, sixty minutes, were permitted to elapse after establishing the wounds, and then 0.2 Gm. of sulfadiazine was implanted in each wound. Sulfadiazine instead of its sodium salt was used because of the higher p_H of the latter. The drug was sterilized by heating to 120 C. in a dry oven for twenty-five minutes. The amount of sulfadiazine

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1. McSwain, B., and Glenn, F.: Sodium Sulfadiazine in Experimental Streptococcus Infection, Arch. Surg., this issue, p. 223.

implanted was obviously an excess as far as ideal conditions for wound healing are concerned; only a small part of the powder was dissolved immediately.

Blood was obtained from the ear veins at hourly intervals for six hours and then twenty-four, thirty-six and forty-eight hours after operation. At no time was there more than a faint trace of sulfadiazine detectable in the blood.

In cases in which death occurred, the time was noted, and postmortem inspection of the wounds and cultures of the heart blood and the wounds were made. In cases in which the animal survived, blood for culture was removed from a vein in the ear one week after operation, the cutaneous sutures were removed, the wounds were inspected, the skin edges were pulled apart, and material was removed for culture.

RESULTS

The wounds of the control animals showed no actual cellulitis; however, they showed local necrosis of the muscle and the fascia for an area

Results of Implantation of Sulfadiazine into Wounds Inoculated with a Culture of a Strain of the Beta Hemolytic Streptococcus

						Positive Cultures					
								Wounds			
		Died		Survival Time		Blood		Right		Left	
Group	Rabbits	No.	Per Cent	Total, Hr.	Average, Hr.	No.	Per Cent	No.	Per Cent	No.	Per Cent
Control	9	9	100	842	93.5	9	100	9	100	9	100
Treated	18										
Five minute interval	6	4	66.6	564	141	3	50	5	83.4	5	83.4
Sixty minute interval	12	10	83.4	1,516	151.6	6	50	11	91.7	12	100

of approximately 1 cm. around the incision, gross autolysis of the muscle segment, a small amount of thin odorless exudate and only loose agglutination of the edges of the skin incision.

No difference could be detected between the appearance of the wounds of the animals treated with sulfadiazine five minutes and those treated sixty minutes after inoculation with the streptococcic culture. However, the wounds of the treated animals differed from those of the controls in that in the former there was less local necrosis, less autolysis of the crushed muscle segment and better healing of the skin and the fascia. The amount of undissolved sulfadiazine present varied from approximately one-half the original amount twenty-four hours after operation to complete absorption one week later.

The mortality rate was lower in the experimental than in the control animals (table). Likewise, the average survival time was longer in the treated animals than in the controls. The fact that the average survival time for the animals treated sixty minutes after inoculation with the

culture was longer (one hundred and fifty-one and six-tenths hours) than that of animals treated five minutes after inoculation (one hundred and forty-one hours) can be explained only on the basis of experimental error. The organism was recovered from the blood of only half the treated animals but from the blood of all the controls. There was a slightly lower percentage of positive wound cultures for the treated animals.

SUMMARY AND CONCLUSIONS

Sulfadiazine implanted into wounds experimentally inoculated with a culture of a strain of the beta hemolytic streptococcus resulted in: (1) decreased mortality rate; (2) increased survival time; (3) lower percentage of positive blood cultures; (4) slightly lower percentage of positive wound cultures; (5) apparent improvement in wound healing.

Although there is experimental evidence that the local implantation of sulfanilamide and its derivatives interferes with the healing of clean wounds,[2] this study indicates that it favors the healing of contaminated wounds.

The favorable effects enumerated were evidently due to the local action of the drug since no more than a faint trace was detectable in the blood.

In one series five minutes was permitted to elapse and in another series sixty minutes between the inoculation of the animal with the streptococcic culture and the implantation of the drug. In these two series no difference was noted in the results obtained; this indicates the full effect of the local implantation of sulfadiazine as long as one hour after the time of contamination.

The action of sulfadiazine was not prevented by the presence in the wound of traumatized muscle.

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2. Allen, H. S., and Mason, M. L.: The Effect of Sulfanilamide on the Rate of Healing of Tendons, to be published.

VALUE OF CHEMOTHERAPY IN THE TREATMENT OF OSTEOMYELITIS

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This communication concerning the clinical effect of sulfanilamide and its derivatives as chemotherapeutic aids in the treatment of the various forms of osteomyelitis contains: (1) a résumé of the technical information necessary for the use of these drugs; (2) a résumé of clinical factual experience; (3) a discussion of these facts based on the causative mechanism, the development and the pathology of osteomyelitis and the biologic mechanism according to which these drugs produce their effects; (4) a summary of the conclusions to which these résumés necessarily lead regarding the efficacy of present day chemotherapy.

TECHNICAL INFORMATION NEEDED IN THE ADMINISTRATION OF SULFANILAMIDE AND ITS DERIVATIVES

General Administration.—(*a*) Administration by Mouth: Administration of sulfanilamide and its derivatives by mouth is the method most commonly employed, and its general principles are so well known that there is no need of repetition. Suffice it to emphasize that in the beginning the drug is pushed so that a concentration of 10 to 15 mg. per hundred cubic centimeters of blood is obtained as rapidly as possible. The method generally used is that of Long and Bliss.[1] Most of the drugs are rapidly absorbed from the gastrointestinal tract in about four hours and rapidly excreted so that the drug should be given frequently and in adequate doses.

(*b*) Administration by Rectum: Evidence shows that sulfanilamide is absorbed from the rectum and the colon whether administered in the form of solutions or suppositories.[2] Solutions give a higher concentration in the blood. There seem to be no marked differences in results when the drug is given by rectum rather than by mouth and nausea is

1. Long, P. H., and Bliss, E. A.: Para-Aminobenzenesulfonamide and Its Derivatives: Clinical Observations on Their Use in the Treatment of Infections Due to Beta Hemolytic Streptococci, Arch. Surg. **34**:351 (Feb.) 1937.

2. Turell, R.; Marino, A. W. M., and Nerb, L.: Studies on the Absorption of Sulfanilamide from the Large Intestine: Results Following the Administration of Suppositories, Ann. Surg. **112**:417 (Sept.) 1940.

practically eliminated by this method. When nausea from administration by mouth is present, the rectal route can be substituted.

(*c*) Subcutaneous Administration: Azosulfamide [3] is the preparation most often used for subcutaneous injection. Absorption is somewhat more rapid, but otherwise there seems to be no difference from the results obtained with the oral method.

Solutions of sulfanilamide can be used for continuous subcutaneous injection. Most investigators [4] have used an 0.8 per cent solution in physiologic solution of sodium chloride. The Council on Pharmacy and Chemistry of the American Medical Association [5] advised a 1 per cent solution made up in physiologic solution of sodium chloride or, better still, in one-sixth molar racemic sodium lactate solution. The same total dosage is employed for parenteral as for oral administration. Either injections at intervals of four to six hours or a continuous injection should be given. Continuous injection is advisable for patients showing severe toxic manifestations. In 1 case in my personal experience use of the method was not continued long enough to be conclusive.

(*d*) Intravenous Administration: Sulfapyridine sodium (the monohydrate salt of 2-[paraaminobenzenesulfonamido]-pyridine) seems to be the drug most suited for intravenous administration. A suitable concentration is most rapidly reached and maintained, and since the method is indicated for patients with especially severe toxic manifestations, large doses are advised. In 18 cases in which intravenous administration was carried out by Whittemore, Royster and Riedel,[6] there was no local or systemic reaction. Nausea occurred in only 1 case; the therapeutic effect was rapid, but there was difficulty in maintaining blood levels constant. I have used this method myself in 1 case of severe cranial osteomyelitis following disease of the frontal sinuses with intracranial complications; the results were negative.

Both the subcutaneous and the intravenous method of administration can be used in the immediate postoperative period and until the drugs can be administered by mouth in order to thwart infection in cases in

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3. Azosulfamide is disodium-4-sulfamidophenyl-α-azo-7′-acetylamino-1′-hydroxynaphthalene-3′, 6′-disulfonate. This substance has been known as prontosil soluble, as prontosil and as neoprontosil.

4. Lockwood, J. S.: Sulfanilamide in Surgical Infections: Its Possibilities and Limitations, J. A. M. A. **115**:1190 (Oct. 5) 1940.

5. Sulfanilamide, report of the Council on Pharmacy and Chemistry, J. A. M. A. **114**:326 (Jan. 27) 1940.

6. Whittemore, W. L.; Royster, C. L., and Riedel, P. A.: Intravenous and Rectal Administration of Sulfapyridine in Pneumococcic Pneumonia, J. A. M. A. **114**:940 (March 16) 1940.

which contamination during operation is likely or in cases of grossly contaminated traumatic wounds involving bone.

(*e*) Administration of Sulfanilamide Dissolved in Plasma: Bécart and Philippe [7] correlated their data with those of previous investigators and noted the value of human blood plasma solutions of sulfanilamide in comparison with total blood and artificial solutions in emergency situations such as are present with military wounds. They stressed the bactericidal and bacteriostatic power of the sulfanilamide-medicated plasma. The mixture can be administered either intramuscularly or intravenously. Since no grouping is required, the method is free from agglutination accidents. The mixture is not affected by conditions of temperature and can easily be transported where it is needed. Its usefulness seems to be enhanced by the observation that plasma does not deteriorate as rapidly as stored blood. The whole subject, however, requires fuller investigation.

Local Use of Chemotherapy.—There are a number of reports in the literature on the effect of the instillation or the application of sulfanilamide and its derivatives in infected bone wounds or fractures either for prophylactic or for therapeutic purposes or for both. I have been able to collect the following:

Key and Burford [8] found that the implantation of crystals of sulfanilamide in experimental contaminated compound fractures in dogs lessened the danger of subsequent development of infection and did not retard healing. It did not, however, permit closing of grossly contaminated wounds. The usual débridement is necessary, as well as a single layer of suture to retain the serum, which becomes saturated with the drug. Immobilization is important. This is much more important, perhaps, in the treatment of military wounds. The method can be useful also in operative bone wounds in which infection might take place.

Furstenberg [9] used sulfanilamide locally in several defects of the skull after operation for osteomyelitis and also in the mastoid cavity. He

> . . . is confident that sulfanilamide has a desirable local influence which hastens repair, lessens the purulent discharge and brings about a more rapid recovery from wound infections. These factors obviously favor the healing of wounds, . . . [and he has] observed a number of mastoids close promptly and com-

7. Bécart, A., and Philippe, B.: Le plasma humain sulfamidé; ses avantages dans la transfusion d'urgence en absence d'un donneur de sang frais, Presse méd. **48**:535 (May 22-25) 1940.

8. Key, J. A., and Burford, T. H.: Local Implantation of Sulfanilamide in Compound Fractures, South. M. J. **33**:449 (May) 1940.

9. Furstenberg, A. C.: Personal communication to the author.

pletely within eleven to fifteen days. Of course, these experiments are in their infancy. . . .

The experience of the Mayo Clinic was given by Mayo and Miller [10] and by Herrell and Brown.[11] Either the crystals or a thick suspension of sulfanilamide was used. Experimental and clinical observations tended to indicate that the local administration of sulfanilamide and its derivatives exerts a definite beneficial effect in the course of infected wounds in a certain number of cases. This is true of postoperatively infected wounds as well as of wounds which may result either from accidental injuries or from injuries incidental to war. They expressed the opinion that the local use of sulfanilamide and its derivatives is of greater value in the prevention of infection than in the treatment of already well established infection. The results are by no means uniform, but they are encouraging enough to justify continuation of the use of the procedure. Among the various cases in which the method was tried there were 2 cases of chronic osteomyelitis.

Spink and Paine [12] reported the following experience:

. . . A number of patients having chronic osteomyelitis had been previously treated with sulfathiazole [2-(paraaminobenzenesulfonamido)-thiazole], administered orally. No apparent beneficial effect was observed. Two patients were treated by placing five grams of sulfathiazole crystals into the infected area. The first patient, a seven-year old female, had osteomyelitis of the tibia. A sinus leading to the bone and the involved portion of the bone were debrided, sulfathiazole was placed in the bony defect. A plaster cast was placed on the extremity. Four days later, the wound was examined through a window cut in the cast. It appeared clean, but staphylococci were isolated from the wound. Additional crystals were placed in the cavity, and the patient was sent home. Three months later examination revealed the wound to have healed, and an x-ray film showed extensive replacement of the defect in the tibia by new bone. A second patient has been treated recently in a similar manner, and further time must elapse before an opinion can be expressed concerning the effect of this therapy.

Combined General and Local Use of Chemotherapy.—At the University of Hamburg, in Germany, a combination of the general and the local use of chemotherapy was tried out by Gottesbüren.[13] Prontosil (compound not stated) was given for its general effect. In complications involving joints it was instilled directly into the joints. Gauze treated

10. Mayo, C. W., and Miller, J. M.: Solution of Sulfanilamide in the Local Treatment of Wounds, Proc. Staff Meet., Mayo Clin. **15**:609 (Sept. 25) 1940.

11. Herrell, W. E., and Brown, A. E.: Solution of Sulfanilamide in the Local Treatment of Wounds, Proc. Staff Meet., Mayo Clin. **15**:609 (Sept. 25) 1940.

12. Spink, W.: Personal communication to the author. Spink, W., and Paine, J. R.: Sulfathiazole in Staphylococcal Infections, Minnesota Med. **23**:615 (Sept.) 1940.

13. Gottesbüren, H.: Die Behandlung der akuten und chronischen Osteomyelitis in der Chirurgischen Universitätsklinik Hamburg-Eppindorf, München. med. Wchnschr. **86**:1378, 1939.

with 10 per cent dimethyldisulfanilamide (N^1,N^1-dimethyl-N^4-sulfanilylsulfanilamide) was used in the wounds. However, no decisive effect was noted.

Adjuvant Action of Other Drugs and Forms of Therapy.—(*a*) Neoarsphenamine: The combination of sulfanilamide with neoarsphenamine has been advised. I have had no experience with this combination, but it seems that such experience as there has been should be further corroborated.

(*b*) Heparin: Possibly because of the work which was done in the treatment of bacterial endocarditis with heparin,[14] Lyons [15] has used heparin as an adjuvant when the ordinary surgical methods and chemotherapy did not produce results. I understand that Lyons has had some good results with the combination of heparin and chemotherapy.

(*c*) Gas Gangrene Antiserum: During the past several years I have used the combination of a prophylactic dose of gas gangrene antiserum with sulfanilamide prior to operations in which there was a possibility of postoperative development of infection by Clostridium welchii with or without other types of infection. No such infection developed in any of the patients. In traumatic bone wounds (civil or military) this combination might be valuable as a prophylactic.

(*d*) Radiotherapy: Radiotherapy and chemotherapy (sulfanilamide) were used by Woodward [16] in combination. This combination of methods has no clinical contradiction, but owing to the small number of cases in which it was employed, the results are inconclusive.

Relative Value of Drugs and Dosages.—There is no absolute agreement as to which of the drugs is best except that sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) seems to work best with pneumococcic infections. My own experience is that, all things considered, sulfanilamide worked best in the general run of cases of surgical infection; and in cases of the latter type of infection none of the derivatives has seemed superior. Apparently it is the custom to change from one to the other drug if no satisfactory results are quickly obtained; but in 2 of my own cases of severe infection in which this change was made, no perceptible difference was noted. Some of the observers have put great reliance on sulfathiazole. Sulfamethylthiazole (2-[paraaminobenzenesulfonamido]-4-methylthiazole) produces too many toxic mani-

14. Kelson, W.: A New Method of Treatment of Subacute Bacterial Endocarditis, Using Sulfapyridine and Heparin in Combination: Preliminary Report, J. A. M. A. **113**:1700-1702 (Nov. 4) 1939.

15. Lyons, C.: Personal communication to the author.

16. Woodward, F. D.: Osteomyelitis of the Skull: Report of Cases Resulting from Frontal Sinus Infections with Staphylococcus, J. A. M. A. **95**:927 (Sept. 27) 1930.

festations; but in a case of mine in which this drug was tried after the others, no superior effect was noted. The use of azosulfamide was advised by Horan and French [17] when maximal concentration is desired in minimal time. The intravenous injection of sulfapyridine sodium is advised for a similar reason; but in 1 of my cases in which this was employed, no effect was noted.

There must be some difference between pneumococcic pneumonia and the general run of surgical infections. In my experience with the latter group of infections, the results have not been anywhere near so striking as the results obtained by physicians in treating pneumonia.

There is no complete agreement as to the best method of administering these drugs. The main index of the sufficiency of the chemotherapeutic agent is the concentration in the blood,[18] and in order to know for certain what this is, blood determinations are necessary. Since the therapeutic aim is to attain a concentration in the blood of 10 to 15 mg. per hundred cubic centimeters as rapidly as possible, all available routes of administration should be used—oral, subcutaneous, intravenous and intramuscular. Intrathecal administration is superfluous because it was noted by Marshall [19] and others that the concentration in the cerebrospinal fluid is close to the concentration in the blood. Not all patients of the same weight respond similarly to identical dosage, and one should therefore vary the dosage with different patients according to the concentration attained in the blood. It is usually advisable to continue therapy for a few days after clinical recovery in order to prevent relapse. Infants tolerate the drugs well; the dose for them is from one third to one half of the adult dose. Children require from one half to three fourths of the adult dose.

EFFECT OF CHEMOTHERAPY ON CERTAIN PHYSIOLOGIC PROCESSES

Effect on Cross Matching Tests.—Because various reports had drifted in that there was difficulty in making cross matching tests after the institution of chemotherapy, an investigation of this problem was made by Kreinin [20] and associates, which confirmed the fact that such difficulty occasionally exists. It was their opinion, however,

17. Horan, V. G., and French, S. G.: Prevention of Mastoiditis: Survey of Six Hundred and Twenty-One Cases of Acute Otitis Media Treated with Sulfanilamide, Lancet **1**:680 (April 13) 1940.

18. Bratton, A. C., and Marshall, E. K., Jr.: New Coupling Component for Sulfanilamide Determination, J. Biol. Chem. **128**:537 (May) 1939.

19. Marshall, E. K., Jr.: The Determination of Sulfanilamide in the Blood and Urine, Proc. Soc. Exper. Biol. & Med. **36**:4221 (April) 1937.

20. Kreinin, S.: The Effect of Sulfanilamide in the Cross Matching of Blood, J. Lab. & Clin. Med. **25**:690-692 (April) 1940.

. . . that the inability to cross match blood following the administration of sulfanilamide is due to changes in the blood brought about by the disease requiring the use of sulfanilamide rather than to the drug itself.

Effect on Bacteriophage Action.—There have been many reports on the effect of antiseptics on bacteriophage. According to Jern and Meleney,[21] bacteriophage is susceptible to, and is destroyed by, certain of the stronger antiseptics. There is a differential susceptibility to some of the weaker antiseptics; the phages of Staphylococcus are regularly more susceptible than those of Bacillus coli. The latter in turn are more susceptible than those of Bacillus pyocyaneus. Therefore, antiseptics in general cannot be used with bacteriophages in the treatment of mixed infections. Zinc peroxide is no exception to this rule.

Sulfanilamide, sulfapyridine and azosulfamide do not interfere with bacteriophage action. It is therefore possible to combine the use of sulfanilamide and sulfapyridine with that of bacteriophage in treating those mixed infections which are caused by hemolytic streptococci combined with staphylococcic or the colon bacilli. This combined method has been used with gratifying results in a number of cases.

Influence on Anesthesia.—I am indebted to Dr. G. H. van Gilluwe[22] of the anesthesia staffs of the Flower and Fifth Avenue Hospitals and the St. Vincent's Hospital for the thought that owing to the diminution of the oxygen content of the body (cyanosis-anoxemia) as a toxic manifestation of the use of these drugs and because of the crippling of the oxygen-carrying function of the blood by the formation of methemoglobin and sulfmethemoglobin, as well as the frequent reduction in the red cell count, it is wise to be more generous with the use of oxygen during the maintenance of inhalation anesthesia in any patients treated with sulfanilamide and its derivatives. He has seen several deaths associated with this situation.

CLINICAL EXPERIENCE WITH CHEMOTHERAPY IN THE TREATMENT OF OSTEOMYELITIS

Acute Primary Osteomyelitis (Direct Infection in Accidental and Operative Bone Wounds).—On following the lead given by the use of sulfanilamide and its derivatives in infected wounds, the prophylactic use of these drugs seems especially indicated in all accidental bone wounds and in all operative bone wounds in which infection might be expected to take place. This should not relieve one of the responsibility of employing all the usual and well tried procedures (i. e., cleansing and débridement for accidental bone wounds and aseptic technic for operative

21. Jern, H. Z., and Meleney, F. L.: Effect on Bacteriophage of Prontylin, Prontosil, Sulfapyridine and Other Antiseptics and Dyes Used in Surgical Practice, J. Lab. & Clin. Med. **24**:1017 (July) 1939.

22. van Gilluwe, G. H.: Personal communication to the author.

wounds) which have endured through many years of successful practice. According to Jensen, Johnsrud and Nelson,[23] the chemotherapeutic drug for prophylactic use should be in crystalline form; Spink and Paine[12] stated that it should be used in an oily suspension or base; Mayo and Miller[10] and Herrell and Brown[11] recommended its use as a thick suspension in a saline solution. The outer wound should be arranged so that the drug will be retained and not eliminated in the discharge from the wound. In spite of the fact that previously ordinary methods have attained success in a high percentage of cases, the helpful action of sulfanilamide and its derivatives should be added prophylactically in suitable cases in view of the good reports in the literature as a consequence of the use of these drugs in infected wounds.

Should the wound communicate with a joint, the chemotherapeutic drug can be instilled directly into the joint.

In certain types of operation (especially those used on the intestines and particularly in posterior operations for carcinoma of the rectum) in which the necessity for resection of the coccyx and the sacrum exists, I have used sulfanilamide prophylactically for several days before the operation for the purpose of lessening or eliminating postoperative osteomyelitis in the stump of the resected bone. It is my distinct impression that the number of such infections has been materially lessened thereby. In addition, I have used sulfanilamide powder locally in the operative fields in which infection is present or likely to occur at the conclusion of the procedure with most satisfactory results.[23a]

Acute Hematogenic Osteomyelitis, with Special Reference to the Long Bones.—The literature does not contain as large a number of reports concerning the use of chemotherapy in cases of hematogenic osteomyelitis of the long bones as it does of the use in cases of extension osteomyelitis of the skull following acute infection of the nose and nasal accessory sinuses or following acute infection of the middle ear with extension to the mastoid process and temporal bone. I herewith give résumés of the more pertinent accounts in the literature which I have been able to find.

In a 10 day old male infant, whose history is reported by Carroll and associates,[24] staphylococcic septicemia developed from an infected umbilicus. No effect was produced by the administration of azosulfamide

23. Jensen, N. K.; Johnsrud, L. W., and Nelson, M. C.: Local Implantation of Sulfanilamide in Compound Fractures, Surgery **6**:1 (July) 1939.

23a. Wilensky, A. O.: The Local Prophylactic Use of Chemotherapy (Sulfanilamide) After Intra-Abdominal Operations Against the Development of Postoperative Infection, M. Rec. **155**:61 (Jan. 21) 1942.

24. Carroll, G.; Kappel, L.; Jones, L.; Gallagher, F. W., and Dirocco, F. W.: Sulfamethylthiazol: A Report of Its Clinical Use in Staphylococcus Septicemia with Apparent Success; Report of Animal Experiments, South. M. J. **33**:83 (Jan.) 1940.

or sulfapyridine. The septic process involved the left knee joint, the right shoulder joint and the right hip joint in succession. Sulfamethylthiazole was then given, and the septic symptoms subsided within twenty-four hours. The infant recovered, but when last seen he had necrosis of the head of the right humerus.

Thornhill, Swart and Reel's [25] case was one of osteomyelitis of the femur with a high grade of toxicity and a growth of Staphylococcus aureus in the blood cultures (5 colonies per cubic centimeter). Sulfanilamide was given from the beginning with a blood concentration of 3.5 mg. The general sepsis as shown by the blood cultures improved slowly, and the blood became sterile only after one month. No real or apparent effect was noted except that seen ordinarily without the use of chemotherapy.

Melton [26] reported 5 cases of osteomyelitis in which the patients were treated with sulfathiazole. In the first case, one of acute osteomyelitis of the radius and the ulna after open reduction of a fracture, there was improvement but no clearing-up after treatment with sulfapyridine. Sulfathiazole was then given to a total of 26 Gm. After each injection the patient complained of headache and vomited, but marked improvement took place. In a case of acute osteomyelitis of the lower end of the humerus, pyrexia persisted after the administration of sulfathiazole but subsided after the drainage of a subperiosteal abscess. In the third case, one of acute osteomyelitis of the upper end of the femur, clearing-up was effected by sulfathiazole. In the fourth case, in which the lower end of the femur was affected, there was pyrexia after drainage; this subsided after treatment with sulfathiazole. In the fifth case there was acute osteomyelitis of the ilium and suppurative arthritis of the hip; the blood culture yielded a growth of Staph. aureus. No improvement was noted after the administration of sulfathiazole, and the blood culture still showed Staph. aureus.

I am inclined to say that chemotherapy had no effect in some of these cases because of the presence of associated lesions (e. g. abscesses, arthritis) which required operation.

Schein's [27] case was one of infection of the spine by B. pyocyaneus. Sulfanilamide was given to the patient for nine days for a total of 27 Gm. A temperature of 106 F. dropped to normal in two days. Administration of the drug was later discontinued because of anorexia, depression and disorientation. One and one-half weeks later there was recurrence of fever; the temperature was up to 102 to 103 F. Sulf-

25. Thornhill, W. A.; Swart, H. A., and Reel, C.: Sulfanilamide in Staphylococcus Septicemia, J. A. M. A. **113**:1638 (Oct. 28) 1939.

26. Melton, G.: Sulfathiazole in Staphylococcic Infections, J. A. M. A. **115**: 471 (Aug. 10) 1940.

27. Schein, A. J.: Pyocyaneus Osteomyelitis of the Spine: Report of Case of Successful Treatment with Sulfanilamide, Arch. Surg. **41**:740 (Sept.) 1940.

anilamide was again given for a total of 34 Gm. The temperature again subsided. A diagnosis of vertebral osteomyelitis was confirmed roentgenographically several weeks later, and healing took place after the patient was put in a spinal brace. The final opinion was that sulfanilamide controlled the original sepsis but did not prevent the localization in the spine.

It is difficult to evaluate this case because toxic symptoms compelled the interruption of chemotherapy and then fever recurred, which in turn subsided after further chemotherapy. There is the possibility that the secondary rise of temperature had a purely local cause and that its subsidence had no relation to the chemotherapy.

Mitchell [28] treated 5 patients for severe acute osteomyelitis with dimethyldisulfanilamide in addition to the ordinary forms of treatment. All did well; the condition of 2 of them had seemed hopeless because of the signs of general sepsis, and the impression is conveyed by the report that the good effect had special reference to this aspect alone.

This experience undoubtedly indicates the good effect of chemotherapy on the general infection per se; this good effect is especially well exemplified in the cases of the 2 patients whose condition seemed hopeless.

Spink [12] treated 5 patients for acute osteomyelitis and septicemia with sulfathiazole. In each instance coincidentally with the administration of the drug the blood cultures became sterile. There was little or no effect on the bone lesion itself. Spink formed the impression that in cases in which the condition is acute chemotherapy (in this case the use of sulfathiazole) may localize the lesion in the bone, thus limiting the extent of the lesion. He stated that according to his still limited experience chemotherapy does not otherwise affect the local lesion once it is present. On the other hand, his experience supports that of others that chemotherapy is and will continue to be of great use in the control of general infection.

In Carey's [29] experience the response to chemotherapy (sulfanilamide) of osteomyelitis caused by the beta hemolytic streptococcus was unpredictable; but chemotherapy (sulfanilamide) should always be instituted because in cases of acute septicemia the infection may be more rapidly localized, the fever reduced and the blood sterilized. Occasionally the chronic form of the disease may be cured by chemotherapy. In cases of staphylococcic osteomyelitis neither sulfanilamide nor sulfapyridine seemed to have much effect, but sulfathiazole seemed to have some definite antistaphylococcic effect.

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28. Mitchell, A.: Treatment of Acute Osteomyelitis by Uleron, Brit. M. J. **2**:1200 (Dec. 10) 1938.

29. Carey, B. W.: Use of Sulfanilamide and Related Compounds in Diseases of Infancy and Childhood, J. A. M. A. **115**:925 (Sept. 11) 1940.

Goldberg and Sachs [30] reported 2 cases in which chemotherapy was used. Sulfanilamide did not have any effect as shown in the blood cultures, which continued positive, but after five days' use of sulfapyridine the blood became sterile. The local lesion was treated by drill holes and the general condition with transfusions. The local signs of inflammation disappeared within three days. Nevertheless, there were roentgen evidences of well marked bone lesions. Goldberg and Sachs commented on the fact that such beneficent sterilization of the blood is seen daily in the absence of chemotherapy.

Chemotherapy has been discarded by Dunkmann,[30a] and he has relied entirely on ordinary surgical procedures in the treatment of osteomyelitis. Apparently chemotherapy has given him no superior results.

The case of Rosenthal and Vogel [31] was one of Staph. aureus osteomyelitis of the humerus treated continuously with 95 Gm. of sulfapyridine. This case is mentioned only to show the harmful effect of the drug; lymphocytic granulocytopenia developed, and the patient, a child, died one month later.

In treating staphylococcic osteomyelitis in general, particularly in the bacteremic phase, Lyons [15] has employed the following measures: (1) surgical management of the suppurative focus, incision and drainage of the focus, excision of the focus or ligation of the major vein draining that focus; (2) administration of sulfathiazole in doses sufficient to maintain a blood concentration of 5 mg. per hundred cubic centimeters; (3) the clinical use of heparin when infections have not been controlled by the procedures already mentioned; he has expressed the opinion that the latter procedure has a definite place in the treatment of osteomyelitis.

My own experience, while limited, has in each instance been informative; I shall give the report of the most illustrative case.

An inflammatory focus developed in the upper end of the tibia of a young boy. Sulfanilamide, sulfapyridine and sulfamethylthiazole were all administered, but the blood culture continued to show a few colonies of staphylococci in spite of the fact that the clinical manifestations seemed better. Then a thrombosed saphenous vein was palpated, and when all of the thrombosed portion was excised, its origin could be traced directly into the involved head of the tibia. Excision of the vein was immediately followed by sterilization of the blood.

In this case there was roentgen evidence of osteomyelitis, and the opinion was expressed by others that the atypical (?) and benevolent course was due to the chemotherapy. I disagree as to this (1) because

30. Goldberg, S. L., and Sachs, A.: Sulfapyridine in Treatment of Staphylococcus Aureus Bacteremia, J. A. M. A. **113**:1639 (Oct. 28) 1939.

30a. Dunkmann, G.: Die Osteomyelitis und ihre Prognose, Ergebn. d. Chir. u. Orthop. **32**:527, 1939.

31. Rosenthal, N., and Vogel, P.: Granulocytopenia Caused by Sulfapyridine in Children, J. A. M. A. **113**:584 (Aug. 12) 1939.

I have had many experiences in which a similar course (with the exception of thrombosis of the saphenous vein) was noted without chemotherapy and (2) because excision of the vein seemed to be the turning point toward recovery. I am inclined to say that chemotherapy had a doubtful value in this case. In any event, since the drug was adequately administered from the beginning of the illness, I feel certain that it had no preventive value with regard to the bone lesion and certainly no value at all in sterilizing the blood.

Primary Osteomyelitis of the Skull.—Primary osteomyelitis of the cranial bones, being a direct infection in a traumatic or an operative wound, is the sort of disease which should receive prophylactic treatment with sulfanilamide and its derivatives both generally and locally. Undoubtedly this use will receive its fullest application in the treatment of military wounds, and this subject is most apropos now. However, no experience is available at present which could guide one except that resulting from chemotherapy applied generally and locally to infected wounds.

Hematogenic Osteomyelitis of the Skull.—An original site for hematogenic infection of the skull is extremely rare, and in most of the relatively few cases that have been recorded the lesions were metastatic either secondary to an original lesion in one of the long bones or simultaneous therewith. I have been unable to find any experience with this condition recorded in the literature, and I have none of my own. Offhand, I should say that whatever experience with hematogenic osteomyelitis in the long bones is available is applicable to hematogenic osteomyelitis of the skull.

Extension Osteomyelitis of the Skull.—Extension osteomyelitis of the skull is intimately bound up with primary nasal accessory sinusitis and with otogenic infection, and all discussion must necessarily take into account the effects of chemotherapy on the preceding infection: (1) the prophylactic effect in the prevention of extension to the cranial bones; (2) the therapeutic effect in the treatment of osteomyelitis itself; (3) the prophylactic effect in the prevention of the intracranial complications which so frequently occur, and (4) the therapeutic effect in the treatment of the latter.

(*a*) After Disease of the Accessory Nasal Sinuses: In the early stages of infection and in cases of mild infection strictly limited in scope to the nasal accessory sinuses, chemotherapy seems to be unnecessary, since in most of these cases spontaneous resolution and cure occur. In cases of severe infection of the nasal accessory sinuses with high fever, chemotherapy seems to act favorably in bringing down the fever according to Kramer [32] and Kulkin.[33] However, Kramer remarked that the

32. Kramer, R.: Personal communication to the author.
33. Kulkin, S.: Personal communication to the author.

"discomfort associated with the administration" of the drug "outweighs in most cases the benefits attained by the reduction in temperature." The indiscriminate use of sulfanilamide and its derivatives should be deprecated, and certainly use by the general public without adequate medical supervision should be restricted. In any event, the course of the infection should be carefully watched and controlled because of the tendency of these drugs to mask the development of any spread into the cranial bones. Further, because of this, it seems to be the consensus that chemotherapy cannot be used in a prophylactic way against the development of any bone complication (e. g., osteomyelitis).

During the early stages of the development of osteomyelitis of the cranial bones, chemotherapy seems to have a somewhat favorable effect on the general clinical manifestations (e. g., fever), even while the bone lesion is advancing. Aside from this, however, the following varied experience is available: The effectiveness of Furstenberg's [9] use of chemotherapy was doubtful because it was necessary to combine surgical intervention with it immediately. At the University of Illinois Fabricant's [34] experience was frankly disappointing; at the Mayo Clinic, according to Adson,[35] chemotherapy was "effective in the early stages of the disease [osteomyelitis] but of little or no value once sequestration had taken place." In Kramer's [32] experience, chemotherapy was fruitless in the treatment of established osteomyelitis. Mosher [36] expressed the opinion that chemotherapy is dangerous because of an undue reliance which may be put on the drug to the exclusion of the necessary surgical procedures. In all reported cases the administration of these drugs has tended to obscure the further development of the clinical and the pathologic picture and the development of dangerous complications.

My own experience parallels that of others in every way: Chemotherapy has not prevented the occurrence of osteomyelitis of the cranial bones. Chemotherapy has tended to mask the development and the spread of infection into the cranial bones. Once osteomyelitis was established, chemotherapy has had no effect, and surgical eradication of the disease has been necessary.

I have had one personal experience with extension osteomyelitis of the skull. The notes are as follows:

> When a young girl 15 years of age returned from a camp at the end of summer, a head cold developed, followed by pain in the right frontal sinus and orbital cellulitis. Intranasal manipulation directed into the nasofrontal duct having proved ineffective, open operation on the frontal sinus was performed by the attending rhinologist, and complete eradication of the frontal sinus with drainage of the orbital abscess was done. At the same time the right antrum and the

34. Fabricant, N. D.: Personal communication to the author.
35. Adson, A. W.: Personal communication to the author.
36. Mosher, H. P.: Personal communication to the author.

ethmoid sinuses were cleared out. Temporary improvement followed, but about two weeks later typical signs of osteomyelitis of the right half of the frontal bone (pain, tenderness, swelling and edema) appeared, and a roentgenogram showed well marked disease of the bone.

The patient was then transferred to my care. I excised the whole of the right half of the frontal bone and revised the site of the previous operation on the frontal sinus. Again there was improvement for about ten days, followed by spread of the disease to the left half of the frontal bone. I operated for the second time and removed about two thirds of the left frontal bone and did a radical operation on the left frontal sinus.

Several days later generalized headache developed, sometimes referable to both mastoid regions; the ears, however, were normal. Gradually thereafter the condition became worse. Neurologic evidences of meningeal irritation followed, and a spinal tap showed fluid containing approximately 150 cells with gram-positive cocci. However, the cocci were never identified, and the cellular content of the spinal fluid at first increased and toward the end diminished. Finally, the patient passed into stupor and coma and eventually, approximately two months after the beginning of the illness, died from an intracranial complication which, because of the atypical generalized signs and the laboratory findings, I thought was encephalitis.

During the entire illness and from its inception the patient was given adequate doses of sulfanilamide and later of sulfathiazole and still later subcutaneous injections of sulfanilamide and finally intravenous injections of sodium sulfapyridine. At no time during the entire illness did the chemotherapy seem to have a clinical effect of any kind; the pathologic condition and the intracranial complication developed and seemed to progress uninfluenced by any of the drugs employed.

(*b*) After Infection of the Middle Ear and the Mastoid Process of the Temporal Bone: Osteomyelitis of the mastoid and petrous portions of the skull occurs as a spread by contiguity from an infection of the lining membrane of the aural and associated cells of the mastoid process. In turn, disease of the mastoid process can spread by contiguity of structure into the squamous or zygomatic processes of the temporal bone and cause osteomyelitis of the temporal bone proper.

Pediatricians report favorable prophylactic results from chemotherapy in the early stages of otitis media; in these stages, however, favorable results are common without chemotherapy. Great caution and careful observation are necessary in these early stages for fear the drug may mask the developing clinical picture.

Bowers' [37] results indicate that when sulfanilamide is regularly given early before bone softening has occurred, operative work is decreased by half. Late treatment doubled the operative indications as compared with those in patients treated early and adequately. In the experience of Horan and French [17] the incidence of mastoiditis after the introduction of sulfanilamide therapy was only 3.4 per cent, compared with the previous 22.7 per cent. They expressed the opinion that the use of

37. Bowers, W. C.: Observations of Seven Hundred and Ninety-Three Cases of Acute Purulent Otitis Media, with Chemotherapy in Three Hundred and Ninety-Six Cases, J. A. M. A. **115**:178 (July 20) 1940.

sulfanilamide and its derivatives will greatly reduce the incidence of mastoiditis and will allow a more conservative attitude to be adopted if mastoiditis develops. Bowers' experience paralleled this: "Chemotherapy has unquestionably added greatly to the confidence of physicians in their ability to conquer acute otitis media and mastoiditis."

Hebble [38] accepted as well established the fact that the earlier the drug is employed in treatment the better the results. Hebble's custom has been to operate on all patients in whom otorrhea continues beyond the sixth week, regardless of any temporarily favorable effects which chemotherapy may show, in order to avoid intracranial involvement and late chronic deafness.

Bowers stated that in general there was poor response to chemotherapy before operation, even when sulfanilamide was employed for longer periods and in larger doses in the absence of toxic symptoms. A somewhat similar response may be expected after operation, but the drug has the tendency to mask certain typical symptoms.

Clinical experience with sulfanilamide at the Massachusetts Eye and Ear Infirmary led Converse [39] to the opinion that sulfanilamide should be reserved for the treatment of spreading or life-endangering infections and that it should not be used as an adjunct to the usual measures for the treatment of infections of minor severity. He gave three reasons for this belief:

1. Premature initiation of drug therapy has made complete clinical evaluation of the patient difficult and has obscured progress of the infection to complicating endophlebitis.

2. There have been recurrence and further spread of the infection after omission of sulfanilamide in patients who clinically appeared to be healed, so that it is clear that the use of sulfanilamide necessitates fairly extensive laboratory studies to confirm the clinical impression of subsidence of the infection.

3. The amount of sulfanilamide required to sterilize a focus of infection is so large that the danger of toxic manifestations necessitates hospitalization of all patients receiving the drug.

Converse stated that the demonstrated evidence creates an obligation because of the aforementioned reasons to continue sulfanilamide therapy, if once begun, until there is bacteriologic as well as clinical evidence of complete subsidence of the infection. Premature cessation of chemo-

38. Hebble, H. M.: Sulfanilamide in Treatment of Acute Infections of the Ear and Mastoid in Infants and in Children: Quantitative Study of Seventeen Cases, Arch. Otolaryng. **31**:808 (May) 1940.

39. Converse, J. M.: Recurrence of Otitic Infections Due to the Beta-Hemolytic Streptococcus, Following Inadequate Sulfanilamide Therapy, J. A. M. A. **113**:1383 (Oct. 7) 1939.

therapy on clinical evidence alone permits exacerbation and recrudescence of infection in a patient with an ill prepared defensive mechanism.

Latency of symptoms is commented on by all observers.[40] Because the apparently too early interruption of chemotherapy has been followed by unheralded intracranial complications after a period in which there was apparently more or less complete cessation of symptoms, Bowers has continued chemotherapy for a week after the subsidence of all symptoms and has had no complications since this method was inaugurated.

Chemotherapy has caused streptococcus mastoiditis to be just as misleading as mastoiditis due to Pneumococcus type III. The picture becomes deceptive; signs of meningitis may become apparent even when the local signs have decreased and mastoid involvement is not suspected, and the potential consequences become more dangerous and difficult to determine.

Chemotherapy in the Treatment of Intracranial Complications of Extension Osteomyelitis of the Skull.—There are more hopeful reports in the literature regarding the use of chemotherapy in the treatment of intracranial complications of osteomyelitis of the skull. According to Kramer,[32] in rhinologic cases,

> . . . the complications due to lymphatic and vascular involvement, with and without meningitis, have responded amazingly to sulfanilamide and its derivatives. For the first time in rhinologic practice, recoveries have been obtained in patients with these complications. [It has been] found . . . absolutely necessary, however, to attack surgically the source of the infection to obtain permanent cure.

At the Mayo Clinic, Adson [35] also has found chemotherapy to be

> . . . of value in controlling and curing a number of patients with meningitis. It is of questionable value once a brain abscess has developed, but judging from . . . experience . . . it is quite effective if given in the early stages of acute encephalitis.

In the cases in which the complications have followed otologic infection, chemotherapy has had a greater trial. Maybaum [40a] and associates use chemotherapy (sulfanilamide) alone in the treatment of otitic complications, viz., meningitis, sinus thrombosis and abscess of the brain. Removal of the bone focus or other localized lesion (extradural abscess) is imperative, but in the presence of extreme bacterial meningitis intensive chemotherapy is advised for twenty-four to thirty-six

40. (*a*) Maybaum, J. L.; Snyder, E. R., and Coleman, L.: Experiences with Sulfanilamide Therapy for Otogenous Infections, with Special Reference to Masking of the Clinical Course, Arch. Otolaryng. **30**:557-575 (Oct.) 1939. (*b*) Smith, H. B., and Coon, E. H.: Meningitis Due to a Hemolytic Streptococcus: Report of Two Cases with Recovery After Use of Prontosil and Sulfanilamide, ibid. **26**: 56 (July) 1937.

hours prior to operation. In the presence of complications, sulfanilamide is given, and any local focus is eradicated. In cases of petrositis chemotherapy is dangerous during the period of observation because of the tendency to mask the clinical picture, but once the diagnosis is made, sulfanilamide should be given in addition to any operative manipulation. This drug is especially useful in cases of continued otitic sepsis, even though localized foci have been surgically eradicated.

Experienced aural surgeons have always been most apprehensive of intracranial complications. Chemotherapy has introduced a peculiar antagonistic effect. On the one hand, chemotherapy may so mask the symptoms that apparently symptomless meningitis may develop; on the other hand, chemotherapy is establishing a dominating place for itself in the successful treatment of meningitis. In the twenty-five years prior to 1936, only 76 recoveries from streptococcic meningitis were reported in the literature; since 1936, over 200 recoveries have been reported. Mortality has dropped from 97 to 35 per cent. This is a great comfort and a signal achievement. Success in treating intracranial complications, according to Maybaum and associates,[40a] follows only when the original focus has been thoroughly eradicated, because while sulfanilamide is effective in clearing body fluids of streptococci, it is not effective when the bacteria are locked up in osseous tissue.

In the only personal experience I have had with intracranial spread of infection (described previously), chemotherapy seemed to have no effect. Sulfanilamide, azosulfamide, sulfathiazole and sodium sulfapyridine were used by mouth, by hypodermic injection, by continuous subcutaneous infusion and by the intravenous route.

Chemotherapy in the Treatment of Dentoalveolar Infections.—Only a few oral surgeons and dentists are ready to make definite statements regarding the use of chemotherapy in the treatment of dentoalveolar infections and their complications. Some, with whom I have discussed the matter, have expressed the opinion that it has been of help.[41] Apparently some dramatic results occur; this is evidenced by a case related to me by Goldberg.[41a]

A young boy 12 years of age had acute infection of the left second upper bicuspid with swelling of the face, a temperature of 106 F. and cyanosis. After extraction of the root, pus was evacuated, and a diagnosis of maxillary sinusitis with possible extension to the cavernous sinus was made. Chemotherapy was employed in connection with proper surgical drainage, and recovery followed.

I have not been able to find any reported experience with the prophylactic use of chemotherapy in the prevention of osteomyelitis of the jaws following dentoalveolar infection. Stern's experience

41. (*a*) Goldberg, H.: Personal communication to the author. (*b*) Winter, L.: Personal communication to the author.

included 4 cases in which osteomyelitis developed despite previous chemotherapy and continued to develop until sequestration occurred.

I am indebted to Dr. L. Stern [42] for the following experience: Topical application has been valuable in diminishing pain, periostitis and lymphadenitis. It reduces the period of postoperative treatment following minor operations (extractions, root end resections and cyst extirpations) from 85 per cent in a control group to 12 per cent in the group treated with chemotherapy. Sulfanilamide was somewhat more effective than its derivatives. Besides reduction of temperature and restriction of swelling no effect of chemotherapy was noted in cases with associated abscess, and operation was always necessary.

COMMENT

Only those cases of acute osteomyelitis due to the ordinary pyogenic bacteria, staphylococci and streptococci will be discussed. Ordinary acute hematogenic osteomyelitis is commonly due to infection by Staph. aureus. Extension osteomyelitis of the skull after infection of the nasal accessory sinuses is more commonly due to streptococci of the hemolytic and nonhemolytic type. Extension osteomyelitis following otologic infection is most commonly due to streptococci and pneumococci. Primary osteomyelitis (infected traumatic wounds of bone) wherever it occurs is due to a variety of organisms depending on environmental and causal conditions. Commonly these organisms belong to the colon groups; and in military wounds they form the commonest cause as a fecal infection due to the unnatural conditions of army life in the field. In considering the effects of treatment with sulfanilamide and its derivatives, the bacterial findings should be kept in mind since the various drugs exhibit different potencies with the various classes of bacteria.

For a proper understanding of chemotherapy it is necessary to review the essential characteristics of bacterial infection both as a general phenomenon involving the body as a whole and as a local phenomenon involving any particular area, tissue or organ of the body—in this instance, bone.

Infection occurs in the animal body in one of the following ways:

1. Local infections. Localized areas of infection occur on the surface of the body (i. e., the skin, the mucosa of the alimentary canal, the lining of the genitourinary tract), and no general effect on the body as a whole is perceptible to the person affected or to the unaided senses of the examiner or is discoverable by any laboratory method. Cultures of the peripheral blood show no growth of any organisms. Equally commonly, only one such episode occurs and is followed by permanent cure; or there is a succession of such episodes separated by intervals of apparently

42. Stern, L.: Personal communication to the author.

complete health. These are minor infections, and the use of chemotherapy in their treatment is not necessary or advisable.

2. Local infection with generalized effect. Localized areas of infection similar to those just described occur, but evidences of varying degrees of intensity are present to show that the body as a whole is affected by the infection. The perceptible evidences include fever with or without chills, subjective symptoms of general intoxication and cultures of the peripheral blood which may or may not show a growth of organisms. Commonly only one such episode occurs—any bacteremia is only temporary—and complete cure follows. Relatively rarely, retrogression of the general infection is interrupted by recrudescence of the infection. Then the infection may progressively increase until the subject is overwhelmed, or secondary retrogression to cure may follow either undisturbed or with further subsequent similar interruption. Chemotherapy may not be necessary or advisable in cases without symptoms of general intoxication and without positive blood cultures. As soon, however, as the latter are present, chemotherapy should be administered intensively because chemotherapy has its greatest effect in the stage of general infection.

3. General infections. Clinical and/or laboratory evidence of general bacterial invasion of the body may occur (1) without any discoverable evidence of the primary local lesion or (2) in the presence of a demonstrable primary local lesion. In this group the general infection dominates the clinical picture either temporarily or permanently and in the majority of the cases is accompanied by bacteremia, demonstrable by culturing the peripheral blood. The number of colonies of growth in the culture plates form a convenient measure of the intensity of the general infection, and a comparison of repeated blood cultures may be used as a measure of the further progression or of any lessening of the infection and of improvement in the clinical picture. Hence the greatest opportunity for chemotherapy exists as the physical and the distribution characteristics of the bacterial invasion most nearly approach test tube conditions and permit intimate contact between bacteria and the chemotherapeutic agent. Clinically, this corresponds to the presence of living bacteria in the blood stream (i. e., bacteremia).

The essential mechanism for such general infection is undoubtedly an infected clot in a vascular channel in which the growth of organisms occurs on that surface of the clot bordering freely circulating blood. The continual shedding of organisms into the circulating blood forms the physical basis for bacteremia (general infection). In actual practice the infected clot may be (1) accessible or (2) inaccessible for surgical ligation or removal.

1. Accessible infected thrombi of this nature as they occur in general surgical practice are part and parcel of thrombophlebitis. Classic

examples of this are jugular thrombosis after mastoid infection of the process of the temporal bone and the occurrence in the case of osteomyelitis reported in this communication.

In actual practice chemotherapy has no sterilizing effect when an infected clot of this sort keeps shedding bacteria into the general circulation. To sterilize the blood, it is necessary to eliminate the offending segment of blood vessel which contains the infected thrombus by excision. The case cited previously presents an almost laboratory proof of this statement.

2. The outstanding grossly observable example of inaccessible infected thrombi is endocarditis with active bacterial growth in the vegetations of the valves. It is true that in cases of general infection without demonstrable local lesions, endocarditis of this kind is frequently present at postmortem examination. Even though chemotherapy has previously been mostly a failure in cases in which the infected thrombi were inaccessible, even when heparin has been added, a number of brilliant recoveries from cavernous sinus thrombophlebitis have recently been reported.

In laboratory practice this endocarditis corresponds to a surface culture (plate or tube) in which bacterial growth heaps itself up on the surface of the medium and does not extend into the depths. All activity and effect of the bacterial accumulation occurs on the surface and is readily counteracted by any fluid medium which may cover it. Such bacterial growth, in contradistinction to that which may be caused to develop in the depths of a culture medium, is easy of access in the maximum degree to any antibacterial agent which may be brought in contact with it so that growth of the organisms is most easily inhibited or totally stopped with or without death of the organisms themselves.

Bacterial growth in the depth of a culture medium parallels growth in the depth of any thrombus; neither is much or at all affected by the superimposed drug. In the depths, bacterial growth continues, perhaps with much diminished activity. Should the drug he removed too soon, bacterial growth in either case eventually reaches the surface and begins to flourish there again—in the test tube as a renewed surface activity, in the thrombus or in a locked-away focus of infection (as in a bone) as a renewed clinical manifestation with recrudescence of symptoms and unexpected or masked continuation of the pathologic process or, perhaps, by the appearance of important complications. This explains why in certain cases chemotherapy is ineffective in preventing continued pathologic changes, why masking of the symptoms and the lesion occurs and is so frequently commented on and why complications are not prevented and make sudden unheralded appearances.

In progressively increasing bacteremia, the increase in the number of bacteria is due to growth in the original vascular clot, to the increment in other such vascular clots as metastatic foci are formed and, possibly,

rarely to growth of the bacteria in the circulating blood stream. The difficulties of successful chemotherapy under such conditions are proportionately increased.

In any case with clinical or laboratory evidence of general bacterial infection, secondary (metastatic) foci occur in various tissues and organs of the body. When local physical conditions are appropriate, any or all of the secondary foci may act in turn as points of departure for additional infection. In cases of osteomyelitis, secondary or metastatic foci of infection in other bones or in other tissues of the body commonly form inportant parts of the total clinical picture. As far as can be learned from the literature, chemotherapy does nothing to prevent the appearance or the development of such metastatic foci.

As a physical phenomenon, infection appears as: (1) a localized area on an external surface of the body (the skin, the mucous membrane of the alimentary canal or of the genitourinary tract, the conjunctivas); (2) a localized area on a surface lining one of the body cavities (the pleural or the peritoneal cavity or the meningeal or the pericardial space); (3) a localized area buried in the depths of a solid tissue organ (muscle or bone) or in a fascial space, or (4) a general bacterial infection, evidenced most commonly by a positive blood culture with or without a demonstrable local lesion.

With infection of the first type, usually, though not always, there is little or no clinical evidence of effects of the bacterial activity on the body as a whole. With the second, third and fourth types, it is the rule to have clinical evidence of the effects of the bacterial activity on the body as a whole. Frequently with the second and third, and always with the fourth, type there is, in addition, laboratory evidence (positive blood cultures) of the presence of bacteria in the peripheral circulation. Chemotherapy as related to the physical phenomenon of infection is successful in direct proportion to the possibility of intimate contact between the chemotherapeutic agent and the bacteria.

A localized lesion may show pathologic anatomic or physiologic effects because of: (1) the presence and the activity of active living bacteria (the effect of chemotherapy on a lesion of this type is not always predictable, but there are many reports in the literature of some striking successful effects); (2) the effect of thrombosis and embolism (this is most marked in a bone in which the physical conditions of the circulation are such that thrombosis [blockage] of a major vessel may deprive a segment of the bone of nutrition, and this mechanically causes necrosis of tissue; chemotherapy has no effect on these purely mechanical consequences); (3) any enlargement of a local lesion bordering on a cavity or space (skull to subdural space, bone to joint) resulting in mechanical bursting of an area of liquefaction with consequent spreading of the infection to the entire surface of the adjacent space or cavity (the effect of chemo-

therapy in the treatment of these accidents is unpredictable and difficult of interpretation).

Any general infection (with or without demonstrable bacteremia) produces pathologic anatomic and/or physiologic effects: (1) by virtue of the production of bacterial toxins of sufficient amount and/or intensity to produce pathologic effects varying from a perceptible but unimportant degree to that in which the entire body is overwhelmed and death follows; (2) by virtue of the production of thromboembolic lesions in various organs and tissues with the production of secondary (metastatic) foci; (3) by virtue of the simultaneous occurrence of both of these mechanisms.

In the treatment of general surgical infections, the effects of chemotherapy have up to now been unpredictable. Many times this is due to the difficulty of reaching the provocative local lesion or even of discovering it. In osteomyelitis, the bone lesion is secondary to a general infection, which in turn is due to some preceding primary lesion (e. g., a furuncle). The demonstrable bacteremia may be due to a continuance of activity in the primary lesion or to activity in the local bone lesion. In any event I have come to know that chemotherapy is not successful when a local lesion provocative of bacteremia is still present and that surgical eradication of such a local lesion is necessary if chemotherapy is to be successful.

Chemotherapy in the Treatment of Hematogenic Osteomyelitis.—Acute hematogenic osteomyelitis is a bacterially infected embolus blocking a more or less important vascular channel in a bone with all of its consequences. In the absence of demonstrable bacteremia or general infection, there are certain local consequences. The least important of the consequences is local bacterial infection; this either is controlled by the proper antibacterial forces of the body or results in an abscess (subperiosteal, with or without extension into the soft parts and intramedullary abscess). The local infection becomes important only when it is communicated in some way to a neighboring joint or to a contiguous cavity (pericardial, pleural, meningeal). The most important local consequence of blockage by a thrombus or an embolus is the disturbance or total exclusion of the blood supply from the corresponding segment of bone supplied by the affected vessel, with consequent necrosis and sequestration; all of this is due to a purely mechanical disability usually not much influenced by the infection. The important thing to remember is that the area so blocked off does not come into contact with the freely circulating blood and cannot be reached by any chemotherapeutic agent contained therein.

Chemotherapy in the Treatment of Chronic Osteomyelitis.—Chronic osteomyelitis and the persistence of open wounds leading down to diseased bone are due to several broad causes: (1) the persistence of infection; (2) the retention of sequestrums (foreign body); (3) the presence

of mechanical conditions which do not permit closure of the wound, and (4) the presence of complicating conditions. The second and third causes are of a purely mechanical nature.

1. Infection persists in small infected thrombi in the diseased area, in small collections of pus enclosed in small bone spaces devoid of proper drainage or in small collections of bacteria locked away in the depths of scar tissue. Access of any chemotherapeutic agent in the blood stream to the local lesion is difficult or impossible because the blood or the lymph supply to such areas is absent or severely limited.

2. Mechanical disabilities in the area of any wound or sinus are uninfluenced by any chemotherapeutic agent. These include sequestrums, insufficient drainage openings, such as a cortical perforation or a canal passing through the thickness of a bone, and a bone cavity with its inability to collapse and permit obliteration of the space.

3. Complicating conditions include especially joint involvement, which operates by adding mechanical disabilities in addition to being a source of reinfection. Both local and general methods of administration of the chemotherapeutic agent are indicated here, but their effect is often unpredictable.

The factors which determine the possibility and efficacy of healing of any acute or chronic osteomyelitis include: (1) the possibility of eradication of the foci of infection by mechanical surgical means or by chemotherapy (because of the absolutely or much diminished blood supply access of the chemotherapeutic agent is not possible or not possible in sufficient concentration); (2) the possibility of revascularization of any compromised bone segment (in proportion as this approaches normal, chemotherapy holds out some possibility of aid); (3) the elimination of any mechanical obstruction to healing (this cannot be influenced by chemotherapy since it is a purely physical disability; but the prophylactic use of these drugs could, perhaps, be advantageous when secondary operations are necessary for the correction or elimination of these mechanical disabilities); (4) the prevention or elimination of any complicating factor (in this phase of the subject the local use of chemotherapy is indicated for complicated infections of neighboring hollow spaces, especially for complicating joint infections; the ordinary general use of chemotherapy is indicated also when complicating joint infections are accompanied by high fever and other signs of general toxicity which are commonly present as a reflection of patent or latent infection).

When bacteria are locked up in the depths of a blood clot (as in a thrombus or an embolus or in part of the body, such as a bone) from which freely circulating body fluids have been excluded by the plugging effect of a thrombus or embolus, the effect of the drug becomes minimal or is entirely absent, and chemotherapy is a failure. This explains the failures in clinical practice, the masking of local signs and the progression

of pathologic changes. Then, too, if part of such an infected clot breaks off or becomes dislodged to travel to and become blocked in a distant part of the body, metastatic lesions can occur and develop in spite of the saturation of the body with the chemotherapeutic drug.

Since in any case of bacterial infection, and especially in one of acute hematogenic osteomyelitis, a most classic example of the latter, the entire pathologic process consists of a general effect on the entire body and a strictly local effect at the point of development of the local lesion, and since the bacteriostatic effect of chemotherapy does not take place in a sequestrated portion from which the general circulating fluids of the body are excluded, it follows that in any of these cases the local lesion can and frequently does remain and continues as a latent or masked phenomenon, even though the general symptoms (e. g., fever, toxicity) have shown marked improvement. This masking effect has been commented on and emphasized by all observers, especially the clinicians.

Chemotherapy in the Treatment of Acute Hematogenic Osteomyelitis.—Since acute hematogenic osteomyelitis is a local manifestation of a general bacterial infection in which the initial stage is marked by positive blood cultures, the only stage in which any chemotherapeutic bacteriostatic or bactericidal effect is to be expected is that in which bacteremia is present. When this effect is obtained, that part of the clinical picture which is caused by the presence of living bacteria in the blood stream (i. e., chills, at least part of the fever, toxicity) is either lessened or entirely eliminated in direct proportion to the bacteriostatic or bactericidal effect produced. In effect this leads to amelioration of the general clinical symptoms so that the clinician is led to believe that the local lesion also is improving *pari passu* with the general improvement.

The best effect of chemotherapy occurs in cases of general infection in which bacteria are being transported in the blood stream. Nevertheless, should additional numbers of bacteria be continuously shed into the blood stream from an infected blood clot, chemotherapy will have no apparent effect on positive blood cultures. I have had such an experience in practice myself, in which the positive blood culture was eliminated only after the infected thrombosed vein was excised. The valuable practical lesson which all of this teaches is that chemotherapy has no lasting effect, unless all local lesions potentially provocative of bacteremia have been thoroughly removed by surgical means. This should always be kept in mind when chemotherapy is employed in the treatment of osteomyelitis.

This points to a prophylactic use for chemotherapy. Should one have in mind an operation in infected territory from which bacteria may be derived into the circulation, a sufficient concentration of a chemotherapeutic agent might succeed in inhibiting the activity of the bacteria and in rendering their immediate destruction possible. I have used this principle in the preparation of certain classes of patients and have suc-

ceeded in eliminating certain postoperative reactions and infections which have hitherto occurred.

Beneficent retrogressive changes are commonly seen and have been commonly noted in the clinical histories of many patients with acute osteomyelitis who in past years and before the advent of the new chemotherapeutic drugs have come under the care of all surgeons. Sometimes these beneficent improvements in the various aspects of the clinical, anatomic and pathologic pictures attained remarkable extents and were most gratifyingly surprising when just the opposite outcome seemed imminent. Such unaided spontaneous favorable outcomes undoubtedly are occurring today and will continue to happen. In the new experience with chemotherapy such results also appear and it remains to be seen in the accumulated experience whether the actual and percentage relations will be different or approximately the same. In any event, in making any conclusion as to the action of any of the new chemotherapeutic drugs in the treatment of osteomyelitis, the possibilities for spontaneous recovery should be remembered.

SUMMARY AND CONCLUSIONS

Sulfanilamide, sulfapyridine, sulfathiazole and sodium sulfapyridine can be administered by mouth, by hypodermic injection and by continuous subcutaneous and intravenous infusion. They can also be instilled locally into a wound, dissolved in plasma and reinjected into the circulation and injected into the subdural cerebrospinal space and lumbar puncture. They can be combined with other drugs, as arsphenamine or heparin, with gas gangrene antiserum, with radiation therapy and with blood transfusions. Each of the drugs seems to have a special affinity for a different group or strain of bacteria. The drugs are rapidly absorbed and quickly excreted, so that the dose must be fairly large and frequently administered. They do not interfere with certain physiologic functions, such as blood groupings, with normal antibacterial activities and with bacteriophage action. When carefully administered and checked by repeated laboratory examinations, the drugs are safe to administer, and gastrointestinal and/or hematologic complications can be entirely avoided or markedly ameliorated.

All of these drugs act by inhibiting the biologic activities of the bacteria, which assume a dormant state (bacteriostasis). Destruction of the bacteria (bacteriolysis) is then accomplished by the ordinary antibacterial agencies of the body, and the drugs must be administered for a sufficient length of time and in sufficient concentration to enable the latter to work adequately; otherwise, bacterial activity is not inhibited, and/or symptoms recrudesce, and the disease increases. The drugs act only by intimate contact with the offending bacteria; hence, they act best and perhaps exclusively when the bacteria are in the circulating blood or in the fluid

content of normal cavities or spaces (e. g., the subdural space). When the bacteria are locked away out of ready contact with the circulating body fluids (as in a bone or within a thrombus or an embolus), little or no effect is produced; hence, all of such foci of infection must be surgically eradicated if chemotherapy is to have the desired effect. The failure to eradicate them leads to failure of treatment, from the start or after temporary improvement, to masking of symptoms, to unperceived symptomless advance of the pathologic process, to unexpected recrudescence of the symptoms and to unheralded complications.

All of these facts are particularly applicable to acute osteomyelitis, especially the hematogenic variety, in each of its typical skeletal distributions. A consideration of these criteria should guide one in the proper application of chemotherapy as an aid in the treatment of this condition.

In cases of primary osteomyelitis, the local use in the wound at first, and later, if necessary, the general use of chemotherapy are indicated. In the treatment of extension osteomyelitis, particularly that of the cranial bones, chemotherapy has met with obstacles so far as the prevention of the spread of the disease and of the occurrence of intracranial complications is concerned; in the latter, however, chemotherapy has shown some wonderful results; but even here experience has shown the absolute necessity of removing all local areas of infection. In cases of acute hematogenic osteomyelitis, chemotherapy is especially indicated in the stage of general infection; and the danger of a progressive hidden pathologic process must be kept in mind.

The results of chemotherapy are not always predictable, owing to the various obstacles enumerated in this communication to the efficient exercise of the bacteriostatic power of the drug, to the occasional difficulty of maintaining the proper concentration of the drug, to the necessity of matching the proper drug to the provocative organism, to the occurrence of certain toxic effects of the drugs themselves and to the difficulty inherent in removing inaccessible foci of infection by surgical means, which is always necessary.

In actual practice, the treatment of osteomyelitis with sulfanilamide and its derivatives has not produced the startling results which it has had in the treatment of some medical conditions, notably the various types of pneumonia. The observed results have varied all the way from the absolutely negative to occasional satisfactory effects; but always the results have been unpredictable; these drugs as a rule have not prevented the spread of the disease or the occurrence of complications and in general surgical practice and especially in the treatment of osteomyelitis, have not been as satisfactory as one could wish Sometimes the proper interpretation of good results is difficult owing to the possibility that such beneficent results have occurred spontaneously, as they have done many times in the past before this form of chemotherapy was available.

EFFECT OF THE ADMINISTRATION OF LIPOCAIC AND CHOLESTEROL IN RABBITS

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If rabbits are fed cholesterol in excessive amounts, a marked and sustained elevation of the blood cholesterol level occurs, and after a few months progressive intimal changes appear in the aorta.[1] Cholesterol and other lipids[2] are deposited in the inner layers of the aorta, and gradually lesions develop which assume most of the characteristics of human arteriosclerosis.[3] These findings suggest that this disease may be the result of some metabolic defect and not a necessary accompaniment of the aging process. The abnormally high incidence of presenile arteriosclerosis in patients with diabetes mellitus supports this view. Here also there is evidence that some disturbance in fat metabolism resulting in sustained hypercholesteremia is involved. Rabinowitch,[4] Joslin[5] and others have demonstrated that high fat diets given to patients with diabetes favor, and that, conversely, low fat–high carbohydrate diets retard, the appearance of hypercholesteremia and arteriosclerosis. The discovery in this laboratory[6] of arteriosclerosis in depancreatized dogs

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with greater incidence than normal for this species presents one more point of resemblance between pancreatic diabetes and diabetes mellitus. The diabetic animals in which this complication developed were maintained on high fat diets with insulin but with inadequate amounts of lipocaic. The role of lipocaic as a second internal secretion of the pancreas has been discussed elsewhere [7] and will not be reviewed here. Continuous administration of lipocaic along with insulin is necessary for the preservation of pancreatectomized animals; and high fat diets increase, and low fat diets diminish, the need for this substance.[8]

The well known facts that some patients with diabetes are not returned to a normal state by the adequate administration of insulin and that the remaining defects are largely attributable to failure of the normal utilization of fat suggested that in these cases a deficiency in lipocaic production might be present and thus play a role in the development of vascular disease.[9] It was to test this possibility that the present experiments were undertaken. A preliminary report was published in 1940.[10] During the course of the work a report appeared by Huber, Broun and Casey [11] in which it was concluded that lipocaic was effective in preventing cholesterol arteriosclerosis and hypercholesteremia in rabbits. The experiments of Steiner [12] and of Baumann and Rusch [13] concerning the effect of choline on cholesterol arteriosclerosis are interesting, since choline has an effect on some phases of lipid metabolism similar to that of lipocaic. Steiner concluded that choline given with cholesterol appeared to delay but not to prevent the appearance of arteriosclerosis in rabbits and that the administration of choline alone produced a resolution of aortic lesions previously induced by cholesterol feeding. Baumann and Rusch, on the other hand, were unable to find any preventive effect of choline on the formation of aortic atheroma and hypercholesteremia or on the deposition of fat and cholesterol in the liver produced by the oral administration of cholesterol.

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EXPERIMENTAL PROCEDURE

A total of 77 young rabbits of both sexes were used for this study. They were kept in metabolism cages and fed a commercial rabbit food[14] which was stated to be a mixture made from alfalfa, oats, barley, corn, soybean, wheat, milk, sodium chloride, calcium carbonate and calcium sulfate and to contain protein (15 per cent), fat (3.25 per cent), carbohydrate (62 per cent) and fiber (12 per cent). Varying amounts of cholesterol (0.25 to 1.0 Gm. per day) and several different preparations of lipocaic[15] were employed. The cholesterol was dissolved in sunflower seed oil according to Leary's method,[8] and a carefully weighed amount was rolled up into a small ball and placed in the back of the rabbit's mouth. Care was taken to make sure that each dose was swallowed.

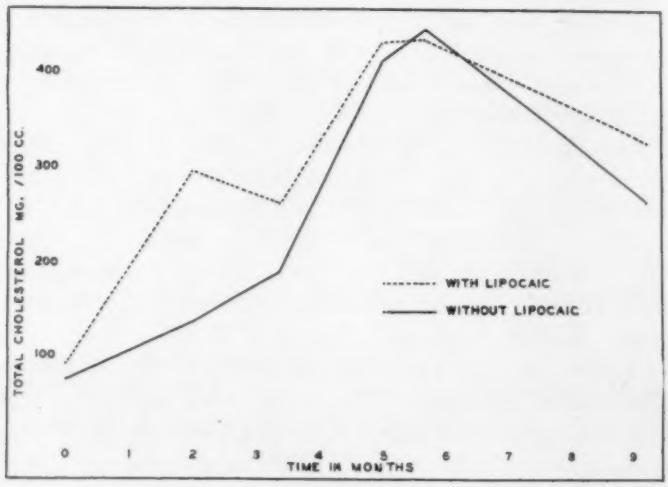

Fig. 1.—Blood cholesterol of rabbits fed cholesterol.

The lipocaic was dissolved in water and placed in the back of the rabbit's mouth with a pipet. Twenty animals received cholesterol alone; 52, cholesterol plus lipocaic, and 5, lipocaic alone. After sixty to three hundred and sixty days of this treatment, the animals were killed and examined. The aorta, the liver, the adrenal glands and the kidneys were studied grossly and microscopically. Blood cholesterol and total lipid determinations were made at intervals throughout the experiment. The livers were analyzed chemically for the cholesterol and the total lipid content. The total lipids were determined by a modification of Bloor's method and the cholesterol by the method of Schonheimer and Sperry.[16]

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RESULTS

The curves in figure 1 illustrate the effect of the oral administration of cholesterol and of cholesterol and lipocaic on the blood cholesterol of rabbits. These curves were constructed from averages of all deter-

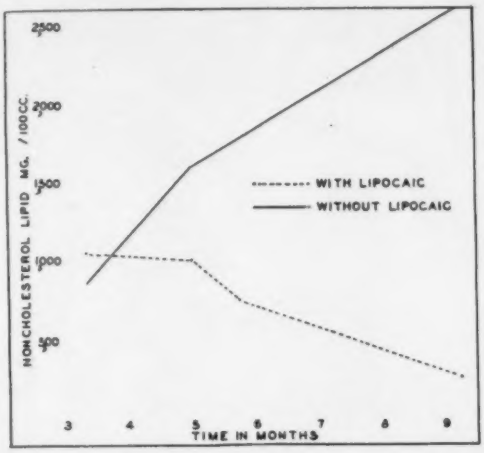

Fig. 2.—Blood noncholesterol lipids of rabbits fed cholesterol.

Fig. 3.—Photograph showing almost identical degree of arteriosclerosis in 2 rabbits receiving cholesterol daily for nine months; 1 of these (rabbit 566) was given lipocaic daily in addition. The adrenal glands of rabbit 566 were somewhat less enlarged than those of the control (rabbit 604).

Fig. 4.—Photomicrograph showing deposition of lipoid material in the greatly thickened intima of the aorta. This rabbit was given 0.25 Gm. of cholesterol daily for five months.

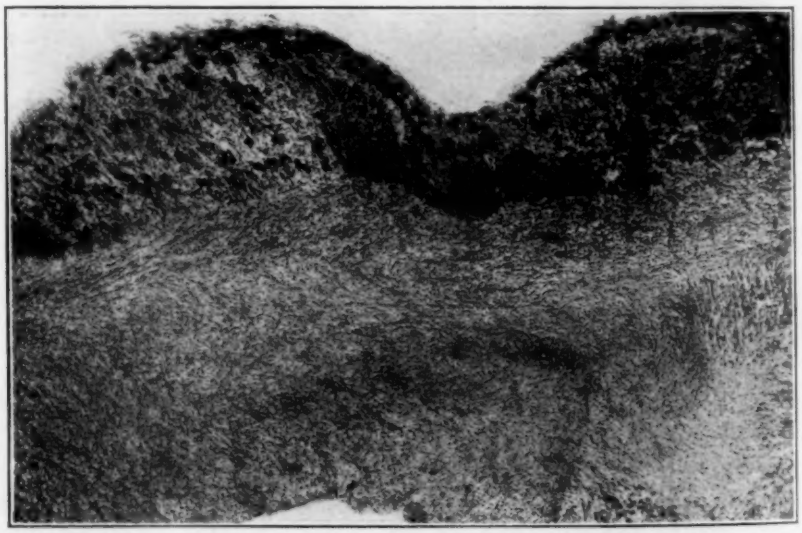

Fig. 5.—Photomicrograph showing similar degree of lipoid deposit in the aorta of a rabbit treated like the rabbit in figure 4 but given lipocaic daily besides.

TABLE 1.—*Effect of Lipocaic on Aortic Lesions Due to Cholesterol*

A. Rabbits Receiving Cholesterol Alone *

Series 1 (1 Gm. of Cholesterol Daily)			Series 2 (0.25 Gm. of Cholesterol Daily)			Series 3 (0.5 Gm. of Cholesterol Daily)			Series 4 (0.5 Gm. of Cholesterol Daily)		
Duration, Days	Rabbits	Extent of Lesion	Duration, Days	Rabbits	Extent of Lesion	Duration, Days	Rabbits	Extent of Lesion	Duration, Days	Rabbits	Extent of Lesion
60	3	Severe	150	1	None	120	1	Moderate	60	1	None
			150	2	Slight	180	1	None	180	1	Moderate
			150	1	Moderate	180	1	Slight	300	1	Slight
			150	2	Severe	310	1	Moderate	330	1	None
						310	1	Severe	330	2	Severe
						240	1	Slight			
						270	2	Slight			

B. Rabbits Receiving Cholesterol Plus Lipocaic

(1 Gm. of Cholesterol Daily; ⅖ Daily Dog Dose † of Lipocaic)			(0.25 Gm. of Cholesterol Daily; ⅖ Daily Dog Dose † of Lipocaic)			(0.5 Gm. of Cholesterol Daily; ½ Daily Dog Dose † of Lipocaic)			(0.5 Gm. of Cholesterol Daily; ½ Daily Dog Dose † of Lipocaic)		
60	2	Slight	150	2	Slight	120	1	Slight	60	2	None
60	5	Moderate	150	4	Moderate	180	1	Slight	180	1	Moderate
60	2	Severe	150	15	Severe	180	2	Moderate	300	1	None
						210	1	Slight	300	1	Severe
						210	1	Moderate	330	1	Slight
						240	2	Moderate	330	1	Moderate
						270	2	Moderate	330	4	Severe
						360	1	Severe			

* Five rabbits were given lipocaic alone, but arteriosclerosis did not develop in any of them.

† A daily dog dose of lipocaic is defined as that amount which will prevent the development of lipocaic deficiency in the pancreatectomized dog. In the first two series of rabbits a crude extract was used, and each rabbit received an extract of 40 Gm. of raw pancreas. In the third series a preparation made by Eli Lilly & Company was used. In the fourth series a purified extract was given, and each rabbit received 50 mg. of dried material.

minations in each of the two series. They show that a marked rise in the blood cholesterol occurs, which tends to diminish somewhat after five or six months. This confirms the observations of Weinhouse and Hirsch.[2] The administration of lipocaic in amounts up to half of that required by the depancreatized dog seemed to accelerate this rise and in general to cause hypercholesteremia to persist somewhat longer than it did in the controls. No preventive effect was discerned, contrary to the findings of Huber, Broun and Casey.[11]

The curves in figure 2 summarize the findings with respect to the effect on the noncholesterol lipids of the blood, chiefly phospholipid and neutral fat. From the hundredth day of the experiment on there occurred

TABLE 2.—*Severity of Aortic Lesions in Rabbits With and Without Lipocaic*

Extent of Lesion	Rabbits Given Cholesterol Alone	Per Cent	Rabbits Given Cholesterol and Lipocaic	Per Cent
None	4	20	3	6
Slight	5	25	8	15
Moderate	4	20	18	35
Severe	7	35	23	44
Total	20	100	52	100

TABLE 3.—*Chemical Analysis of Livers of Rabbits in Series 4*

	Livers of Rabbits Given Cholesterol	Livers of Rabbits Given Lipocaic and Cholesterol	Livers of Rabbits Given Lipocaic
Average liver weight	120 Gm.	130 Gm.	95 Gm.
Average total cholesterol	1.13%	0.65%	0.29%
Average total lipid	7.4 %	5.18%	4.5 %

a progressive rise in this fraction in the animals receiving cholesterol alone. Weinhouse and Hirsch [2] also observed this coincident increase in noncholesterol lipids, the phospholipid being increased seven, the neutral fat five, and the total lipid eleven times above the normal value. The addition of lipocaic to cholesterol produced a striking change, of which the explanation is at present obscure. While the blood cholesterol rose rapidly in these animals, the noncholesterol lipid fell. At nine months, the average noncholesterol lipid value in the first group was 2,600 mg. per hundred cubic centimeters; in the group receiving lipocaic it had fallen 250 mg. per hundred cubic centimeters.

The data on the incidence of arteriosclerosis and the effect of prophylactic lipocaic therapy are given in table 1 and summarized in table 2. It is evident that lipocaic had no beneficial effect either in delaying the onset or in modifying the severity of the lesions (figs. 3, 4 and 5).

Table 3 presents the results of the chemical analysis of the livers in the three series of rabbits. Definite increases in cholesterol and total lipid content are produced by the oral administration of cholesterol, but this change is largely prevented by lipocaic.

COMMENT

The failure of lipocaic to prevent or to modify cholesterol-induced arteriosclerosis in rabbits in the experiments reported is doubtless of limited significance. The pancreas of each of these animals was intact, and presumably its internal secretory function was effective. It is clear that this species metabolizes cholesterol and fats with difficulty, since these substances do not ordinarily constitute a material part of the diet. However, the fact that the rise in the noncholesterol lipid fraction of the blood was entirely prevented and that the deposition of cholesterol and fats in the liver was greatly decreased proves that lipocaic is able to influence the fat metabolism of rabbits. Failure to prevent the deposition of cholesterol and lipids in the intima of the aorta might therefore be due to inadequate dosage or to the method of administration. The answers to these questions must await the development of more potent preparations of lipocaic.

CONCLUSIONS

The oral administration of cholesterol to rabbits produces sustained hyperlipemia, hypercholesteremia, arteriosclerosis of the aorta and accumulation of cholesterol and fat in excessive amounts in the liver and the adrenal glands.

The simultaneous oral administration of lipocaic in amounts up to half of that required daily by the depancreatized dog prevents a rise in the noncholesterol fraction of the blood lipids and also the deposition of fat and cholesterol in the liver but has no effect on hypercholesteremia and arteriosclerosis caused by the oral administration of cholesterol.

CONVULSIONS DURING GENERAL ANESTHESIA

REPORT OF A CASE

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Convulsions or violent involuntary muscular contractions which are occasionally noted in patients during anesthesia induced with ether constitute a definite clinical entity. They cause the anesthetist a great deal of anguish until they are controlled since the death of a patient during a seizure on the operating table is not rare. Lundy [1] reported a mortality rate of 18.97 per cent in a series of 144 cases. Payne [2] calculated the mortality rate to be 23 per cent. Woolmer and Taylor [3] stated the mortality rate to be about 50 per cent. The frequency of ether convulsions is said to be between 1 in 5,000 and 1 in 10,000. Recently reports have been appearing in the literature regarding convulsions during anesthesia induced with divinyl ether.[4]

A sequela equally as tragic as death is complete loss of the mind; this occurred in Weber's [5] case. His patient was a child of 4 years who had convulsions while he was under ether anesthesia during appendectomy.

Although much has been written on the subject since Wilson [6] and Pinson [7] reported the first cases in 1927, no satisfactory solution of the problem has been presented. The factors which have been suggested

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as causing or contributing to ether convulsions are legion and are frequently contradictory.

Nosworthy [8] and Sykes [9] mentioned that the seizures occur almost exclusively in children. Clarke [10] suggested sex susceptibility, stating that the condition is more common in female patients. Toxemia and septicemia are commonly named as predisposing factors.[11] Rovenstine [12] considered trauma to play a part. A. J. D. Smith,[13] Hadfield,[14] Wright [15] and Hewer [16] expressed the opinion that elevation of temperature may be a factor. F. W. G. Smith [17] stated his belief that heat stroke played an important part in Wright's [18] case in which Wright was able to control the convulsions by spinal anesthesia and pentobarbital sodium. In this connection it is interesting that overdosage of atropine has generally been implicated by British anesthetists.[19] Sington [20] questioned the influence of this factor, however, for he observed no convulsions in children over 6 years of age who received 1/80 grain (0.00075 Gm.) of atropine by mouth.

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Fairlie,[21] Pinson[22] and Shipway[23] expressed the belief that the technic of administration of the anesthetic must enter into consideration of the causes of convulsions. It also has been suggested by numerous workers[24] that unnecessary depth of anesthesia may play a part. Laurie,[25] on the other hand, stated that too light anesthesia is a more likely cause. Hadfield[14a] and others[26] mentioned the importance of impurities in the ether. They were unable to explain why ether convulsions were not reported in the literature before 1926. Rood and Webber[27] expressed their opinion that impurities in ether are the result of mixing old residues with fresh ether in the anesthetic machine.

That the answer to the problem may lie in the patient is a possibility which has not been overlooked. Kemp[28] and King[29] thought that some patients possess an idiosyncrasy for ether or a predisposition to convulsions. This is in itself a vague statement, and many authors[30] have attempted to shed light on the nature of this predisposition to ether

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24. (*a*) Ashworth, H. K.: Ether Convulsions, Brit. M. J. **1**:851 (April 20) 1933. (*b*) Blomfield, J.: Convulsions During General Anesthesia, ibid. **1**:1095 (June 20) 1931. (*c*) Cook, B. E.: Ether Convulsions, ibid. **2**:679 (Oct. 10) 1931. (*d*) Corfield, C.: Ether Convulsions, ibid. **1**:1052 (May 18) 1935. (*e*) Courts, A. C. S.: Ether Convulsions, ibid. **1**:959 (May 21) 1932. (*f*) Hewer, C. L.: Recent Advances in Anesthesia and Analgesia, Philadelphia, P. Blakiston's Son & Co., 1932, pp. 41 and 47. (*g*) Thomas, L. K., in Discussion on Late Ether Convulsions, Proc. Roy. Soc. Med. (Sect. Anaesth.) **21**:1705 (May 4) 1928. (*h*) Boyle.[11b]

25. Laurie, W. S.: Convulsions During Surgical Anesthesia, Brit. M. J. **1**:1002 (June 6) 1931.

26. (*a*) Fairlie, H. P.: Ether Convulsions, Brit. M. J. **1**:1195 (June 28) 1930. (*b*) MacKenzie, J. S.: Convulsions During Surgical Anesthesia, ibid. **1**:440 (March 14) 1931. (*c*) Sykes, W. S.: Modern Treatment Anaesthesia, New York, W. W. Norton & Company, 1932, p. 87. (*d*) Walton, A. C. R.: A Note on Ether Convulsions, Brit. M. J. **2**:8 (July 7) 1928. (*e*) Wilson.[11e] (*f*) Hewer.[26]

27. Rood, F. S., and Webber, H. N.: Anaesthesia and Anaesthetics, New York, William Wood and Company, 1930, pp. 134-135.

28. Kemp, W. N.: Unusual Complications of Surgical Anesthesia Under Ether, Brit. J. Anaesth. **10**:145 (July) 1933.

29. King, H. J.: Convulsions Under Ether Anesthesia, Am. J. Surg. **30**:182 (Oct.) 1936.

30. (*a*) Kemp, W. N.: Tetany During Ether Anesthesia, Anesth. & Analg. **12**:1 (Jan.-Feb.) 1933. (*b*) Sears, J. B.: Late Ether Convulsions: Report of Two Cases, J. A. M. A. **100**:1150 (April 15) 1933. (*c*) Hadfield.[14a]

convulsions. After a study of "thymic deaths," Waldbott [31] suggested that ether and general anesthesia may be the source of allergic anaphylactic manifestations. It appeared to McDonagh [32] that the actual state of the patient's protein particles before the anesthetic is administered must play a part in the production of toxic symptoms. He based this statement on the theory that anesthetic substances act by subjecting protein particles in the plasma to sudden dehydration and then to equally sudden hydration. Hyperirritability of the nervous system has been considered as a factor by Haworth [33] and F. W. G. Smith.[17] Rosenow and Tovell [34] attributed the convulsions to a neurotoxin or poison produced by a streptococcus, which is present in amounts which are insufficient to cause spasms but which in the presence of general anesthesia are sufficient to initiate convulsions. Lundy [1] stated that this offers the most promising explanation. Mousel [35] reported convulsions occurring in a child who had a neurotropic strain of streptococcus in the throat. The child was anesthetized again two weeks later. At this time cultures yielded no growth, and the anesthesia was uneventful.

Haworth [36] considered cerebral anemia as a factor and reported cessation of convulsions in a case after the foot of the bed had been elevated. On the other hand, Clarke [10] and Daly [37] suggested the possibility that increased vascularity of the cerebral cortex, especially of the rolandic area, may play a role. Hewer [24f] concurred in this opinion, and Woolmer and Taylor [3] thought that this increased vascularity may play a part. Jirka and Hofrichter [38] mentioned that some cases have been reported in which autopsy revealed a tumor of the brain, which usually showed hemorrhage as the primary cause of the convulsions.

The composition of the blood has been fairly well investigated in a search for the cause of ether convulsions. Sears [30b] and others [39]

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31. Waldbott, G. L.: Late Ether Convulsions, J. A. M. A. **100**:1557 (May 13) 1933.

32. McDonagh, J. E. R.: Convulsions During General and Local Anesthesia, Brit. M. J. **2**:1118 (Dec. 10) 1927.

33. Haworth, J.: Convulsions During Ether Anesthesia, Brit. M. J. **2**:400 (Aug. 29) 1931.

34. Rosenow, E. C., and Tovell, R. M.: Etiology of Muscular Spasms During General Anesthesia, Am. J. Surg. **34**:474 (Dec.) 1936.

35. Mousel, L. H.: An Unusual Case of Convulsions Under Anesthesia, Proc. Staff Meet., Mayo Clin. **15**:33 (Jan. 17) 1940.

36. Haworth, J.: Ether Convulsions, Brit. M. J. **1**:1156 (June 18) 1932. Footnote 33.

37. Daly, A.: Ether Convulsion: A Note as to Treatment, Brit. J. Anaesth. **9**:68 (Jan.) 1932.

38. Jirka, F. J., and Hofrichter, F. C.: Convulsions Under Anesthesia with a Report of Four Cases, Illinois M. J. **75**:549 (June) 1939.

39. Josephs, H.: Fasting as a Cause of Convulsions, Am. J. Dis. Child. **31**: 169 (Feb.) 1926. Wilson.[11e]

described hypoglycemia as a cause. A disturbance of calcium metabolism has been mentioned by Hudson [40] and Raab.[41] Fraser [42] considered ketosis important.

Riddell [43] and Corfield [24d] thought that the convulsions were due to giving oxygen with ether. Mennell [44] suggested hyperoxygenation as the primary factor, but Sapwell [45] and McDonald [46] denied this as a possibility. Smith [13] considered impurities in the oxygen to have some importance.

Gwathmey,[47] Clement [48] and Schreiber [49] expressed the opinion that anoxia is the cause, and Guedel [50] said that if anoxia is a factor, it is of the histotoxic type. Bradshaw [51] reported a case in which determinations of the blood oxygen were made; he found the oxygen capacity decreased to 14.6 volumes per cent and the oxygen saturation to 47.3 per cent. A. J. D. Smith [13] stated that if analyses for oxygen had been made in cases of ether convulsions a clue to the cause might have been found. Hoseason [52] stated his belief that it is possible for lack of oxygen to play a part, even though the blood may be fully saturated with oxygen, if owing to the low carbon dioxide tension the dissociation of oxygen is inhibited. In discussing the signs and symptoms suggestive of lack of oxygen, Waters [53] mentioned muscle twitchings and contractions as a sign prone to occur in the operating room. Bailey [54] reported 2 cases in which patients with convulsions occurring during ether anesthesia showed definite signs of a respiratory depression.

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40. Hudson, R. V.: The Cause and Prevention of "So-Called" Ether Convulsions, Brit. J. Anaesth. **13**:148 (July) 1936.

41. Raab, A.: Convulsions During Ether Anesthesia, Anesth. & Analg. **15**:295 (Nov.-Dec.) 1936.

42. Fraser, L.: Convulsions During Surgical Anesthesia, Brit. M. J. **1**:562 (March 28) 1931.

43. Riddell, L. A.: Ether Convulsions, Brit. M. J. **2**:834 (Nov. 3) 1934.

44. Mennell, Z., in Discussion on Late Ether Convulsions, Proc. Roy. Soc. Med. (Sect. Anaesth.) **21**:39 (Aug.) 1928.

45. Sapwell, J. I.: Ether Convulsions, Brit. M. J. **2**:42 (July 5) 1930.

46. McDonald, N., in Discussion on Late Ether Convulsions, Proc. Roy. Soc. Med. (Sect. Anaesth.) **21**:40 (Aug.) 1928.

47. Gwathmey, J. T.: Ether Convulsions, Lancet **1**:1369 (June 25) 1927.

48. Clement, F. W.: Convulsions During Anesthesia, Anesth. & Analg. **7**:72 (March-April) 1928.

49. Schreiber, F.: Cerebral Anoxia and Anesthesia, J. Michigan M. Soc. **38**:1050 (Dec.) 1939.

50. Guedel, A. E.: Inhalation Anesthesia, New York, The Macmillan Company, 1937, p. 63.

51. Bradshaw, H. H.: Impurities in Ether, Am. J. Surg. **45**:511 (Sept.) 1939.

52. Hoseason, A. S.: Ether Convulsions, Brit. J. Anaesth. **13**:142 (July) 1936.

53. Waters, R. M.: Anoxia: The Anesthetist's Point of View, J. A. M. A. **115**:1687 (Nov. 16) 1940.

54. Bailey, H.: Ether Convulsions, Brit. M. J. **1**:222 (Aug. 17) 1940.

That a lack of carbon dioxide is a possible cause has been considered by Kemp.[28] Collip and Backus[55] and Kemp[56] also suggested a deficit of carbon dioxide and alkalosis as the responsible factors. On the other hand, Bashall[11a] and others[57] considered accumulation of carbon dioxide as a cause. Overbreathing was mentioned by Grant and Goldman,[58] and Courts[24e] asked whether hyperventilation might not play a part.

Finally, Cassels, Becker and Seevers[59] held the opinion that pyrexia and numerous other factors, particularly those which produce metabolic acidosis, increase cerebral irritability to such a level that respiratory acidosis rapidly induced, whether from respiratory depression, rebreathing or the administration of carbon dioxide, serves as an adequate stimulus to induce convulsions during anesthesia. It is possible that no single cause in the foregoing list is alone responsible for these convulsions, but that, as Cassels, Becker and Seevers[59] and Mousel[60] suggested, the convulsions may result from the interaction of two or more abnormal factors.

Although authorities differ widely regarding causation, they are in singular agreement as to the clinical picture. The patient is usually an infant or a young child; rarely, a young adult. Generally the patient is suffering from acute infection with moderate elevation of temperature. Ether is most frequently the anesthetic, although a few cases have been reported in which divinyl ether was used. Induction may be simple or difficult. One of the first untoward signs is a rapid increase in the respiration; this tends to become labored as anesthesia progresses. The first definite sign, however, is twitching about the face, usually beginning above the eyes. The pupils at this time will be widely dilated, inactive to light, with the eye centrally fixed. The twitching then spreads to the facial, neck and shoulder muscles, from here to the arms and the abdomen and finally to the legs. As the spasm spreads, it becomes more violent and sustained. The convulsions are both clonic and tonic and may become so severe that operation is impossible.

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55. Collip, J. B., and Backus, P. L.: The Effect of Prolonged Hyperpnoea on the Carbon Dioxide Combining Power of the Plasma, Am. J. Physiol. **51**:568 (April) 1920.

56. Kemp (footnotes 28 and 30*a*).

57. (*a*) Bull, L. J. F.: Convulsions Occurring During Surgical Anesthesia, Brit. M. J. **2**:471 (Sept. 10) 1927. (*b*) Dickson, D. C.: Convulsions During Anesthesia, ibid. **2**:613 (Oct. 1) 1927. (*c*) Pinson, K. B.: General Convulsion Under Ether, ibid. **2**:277 (Aug. 10) 1929. (*d*) Footnote 7.

58. Grant, S. B., and Goldman, A.: A Study of Forced Respiration, Am. J. Physiol. **52**:209 (June) 1920.

59. Cassels, W. H.; Becker, T. J., and Seevers, M. H.: Convulsions During Anesthesia, Anesthesiology **1**:56 (July) 1940.

60. Mousel, L. H.: Ether Convulsions, Proc. Staff Meet., Mayo Clin. **14**: 285 (May 3) 1939.

Previous to the violent contractions, the color is usually good; but as the seizures continue, cyanosis of varying degree sets in. Hypersecretion of mucus is a prominent feature and necessitates suction to keep the airway patent. The temperature rises to as high as 105 or 107 F. In the cases in which death occurs immediately, respiration ceases after five or fifteen minutes, and deep cyanosis develops. The heart will stop after a short interval. The primary convulsive seizures may disappear, but the patient may fail to recover consciousness on return to his room. At this time the urine is usually strongly acid and may contain casts, albumin and acetone.[9] Death may occur later with bronchopneumonia as the immediate cause. Dramatic recovery may ensue, even in the most severe cases, but transient or permanent mental disorders may result.

These convulsions are not to be confused with the muscular twitchings which occur during the induction of anesthesia with a mixture of nitrous oxide and oxygen and which subside as soon as the oxygen is increased. During the induction of anesthesia with ether, one frequently observes clonic spasms of the legs and arms; however, these usually last for only a short time. These also differ from the true ether convulsions, which occur only after onset of surgical anesthesia and frequently not until the end of the operation.

The pathologic nature of ether convulsions is not definitely known since few autopsies have been reported. No gross lesion suggesting a cause for the convulsions appears to have been observed. F. W. G. Smith [60a] stated that extreme cerebral congestions occur and that edema of parts of the lungs is a common finding. In the case reported by Schnedorf, Lorhan and Orr [61] these same gross changes were present, but histologically, cerebral anoxic changes were observed.

The treatments advocated for ether convulsions are as numerous as the theories advanced for their cause. It is generally agreed, however, that time is a major factor in establishing a favorable prognosis. Wilson [11e] recommended the use of 50 per cent dextrose intravenously. Raab [41] and Hoseason [52] advised the intravenous injection of 10 cc. of a solution of calcium gluconate followed by a solution of dextrose. Lundy [1] suggested that the convulsions can usually be controlled by the use of a barbiturate intravenously. Rosenow and Tovell [34] concurred in this opinion. Dodd [62] has used evipan (sodium salt of *n*-methyl-C-C-cyclohexamyl-methyl barbituric acid); and Daly [19] suggested that this is

60a. Smith, F. W. G.: Late Ether Convulsions, Irish J. M. Sc., September 1936, p. 577.

61. Schnedorf, J. G.; Lorhan, P. H., and Orr, T. G.: Problem of Anoxia in Surgical Anesthesia: Report of Experimental and Clinical Cases and Review of the Literature, Arch. Surg. **43**:169 (Aug.) 1941.

62. Dodd, H. G.: Ether Convulsions Controlled by Evipan, Brit. J. Anaesth. **14**:167 (July) 1937.

probably the safest treatment if all others fail. Chadwick [63] stated his belief that evipan is more satisfactory in children than pentobarbital sodium, which requires accurate dosage and slow rate of administration. Cook [64] used pentothal sodium for the control of convulsions. Wyatt [65] outlined a definite program for combating this clinical syndrome as follows: (1) A soluble barbiturate should be at hand whenever a child is to be operated on for an acute septic process; (2) chloroform, oxygen and carbon dioxide should be readily available; (3) a solution of calcium gluconate or a 50 per cent solution of dextrose for intravenous use should be provided. Hoseason [52] recommended the administration of a calcium compound or the intravenous injection of any hypertonic solution. Lundy [1] stated that as to the selection of anesthesia in cases of profound toxemia it might be better to use spinal, infiltration or block anesthesia or to use avertin with amylene hydrate to produce basal anesthesia rather than to use only an inhalation anesthetic. Laurie [25] also stated his preference for spinal rather than general ether anesthesia. Wilson,[11e] however, expressed the view that in the majority of cases ether convulsions can be prevented by the administration of dextrose in a solution of sodium chloride preoperatively to toxemic patients. A suggested outline of treatment would comprise the following essentials: (1) careful selection of anesthesia for the acutely ill toxic patient, with spinal or basal anesthesia the anesthesia of choice; (2) administration of dextrose in a solution of sodium chloride before operation; (3) moderate dosage of depressant drugs; (4) administration of oxygen; (5) intravenous use of a barbiturate, preferably evipan if convulsions develop; (6) keeping the airway patent; (7) cessation of operation until convulsions are under control.

REPORT OF CASE

The patient was a boy, aged 14 years and weighing 190 pounds (86.2 Kg.). At birth he weighed 16½ pounds (7.3 Kg.), and forceps were required for delivery. As a result Erb's paralysis of the right side developed. The past history was essentially noncontributory except for frequent colds and fevers. On admission to the hospital, the patient had a temperature of 101 F., a pulse rate of 86 and a respiration rate of 22; the blood pressure was 128 systolic and 70 diastolic. A diagnosis of acute appendicitis was made. One fourth of a grain (0.016 Gm.) of morphine sulfate with 1/150 grain (0.0004 Gm.) of atropine sulfate was given at 6:40 a. m. as preliminary medication.

63. Chadwick, T. H.: Evipan Sodium Treatment of Ether Convulsions, Brit. M. J. **1**:1252 (June 20) 1936.

64. Cook, W. B.: Convulsions Associated with Nitrous-Oxide-Ether Anesthesia, Northwest Med. **39**:182 (May) 1940.

65. Wyatt, O. S.: Convulsions in Children While Under Ether Anesthesia, Minnesota Med. **23**:101 (Feb.) 1940.

Anesthesia induced by nitrous oxide, oxygen and ether was started at 7:42 a. m., and the operation was begun at 7:55. Up to this time 40 cc. of ether had been given; the carbon dioxide absorption technic was used with a pharyngeal airway in place. The respiration at this time was quiet and regular at a rate of 32. The pulse rate was 72. The peritoneum was opened at 8:05. Shortly after this the pupils dilated, and the breathing became stertorous and labored. Anesthesia was lightened with improvement of the respiration and the general condition of the patient. At this time the surgeon requested deeper anesthesia because of the patient's muscular rigidity. Relaxation was obtained by giving more ether, and the appendix was delivered. The respirations again became labored and rapid, and the pulse rate rose to 120 but remained of fair quality. At 8:30, twitchings of the forehead were noted, and there was profuse frothing at the mouth. Oxygen and calcium gluconate were given at 8:43; this controlled the convulsions so that the peritoneum and the fascia could be closed. At 8:45, a second series of convulsions began, and the patient became markedly cyanotic with an irregular pulse. Calcium gluconate, coramine (a 25 per cent solution of pyridine betacarboxylic acid diethylamide) and oxygen were given without result. Evipan sodium (3 cc. of a 10 per cent solution) was given intravenously. Immediately, the convulsions began to lessen in severity, and when 4 cc. had been given, the respirations became quiet, the convulsions stopped, and the color began to improve. At 9:05, the convulsions were under control; the pulse rate was 140, the color was fair, and the skin was moist and warm. The rectal temperature at this time was 104.6 F. The patient was returned to his room in fair condition. Late in the afternoon of the same day, the temperature was 102.6 F., the pulse rate was 124, and the respiration rate was 24. The urine was alkaline, and acetone was strongly present on the breath; this was determined by the method of Roth,[66] the use of which for surgical patients has been reported by Lorhan.[67] The patient was restless for the remainder of the day and at times delirious. He also had hallucinations. The following day he had severe headache and marked diarrhea; however, both of these yielded to treatment. Later convalescence was uneventful.

COMMENT

The following discussion is concerned with showing the relation between ether convulsions and cerebral anoxia. In this case toxemia was present with a slight elevation of temperature. One fourth of a grain (0.016 Gm.) of morphine as premedication was probably too much, for McClure, Hartman, Schnedorf and Schelling[68] found that narcotics, and particularly morphine, tend to produce anoxia of the histotoxic type. With the administration of $\frac{1}{150}$ grain (0.0004 Gm.)

66. Roth, P.: Scope and Utility of Tests for Carbon Dioxide Tension and Acetone in Alveolar Air in Relation to Surgery and Anesthesia, Anesth. & Analg. **6**:266 (Dec.) 1927.

67. Lorhan, P. H.: Determinations of Acetone in Expired Air: Its Value in Anesthesia and the Surgical Patient, Anesth. & Analg. **17**:316 (Nov.-Dec.) 1938.

68. McClure, R. D.; Hartman, F.; Schnedorf, J. G., and Schelling, V.: Anoxia: A Source of Possible Complications in Surgical Anesthesia, Ann. Surg. **110**:835 (Nov.) 1939.

of atropine, a moderate dose for a patient 14 years of age, hyperthermia may have occurred. There is complete agreement [69] that atropine can play a large part in the retention of heat in the body. Guedel [50] stated that for each degree of fever the metabolic rate is increased about 7.5 per cent. With this increase of temperature there occurs an increase in metabolism, and the oxygen requirement is greater.

Ether anesthesia is known to increase the rate and the depth of respiration and then the respiratory exchange [70] Haldane [71] found that these changes lower the alveolar oxygen tension, thus decreasing the oxygen saturation of the blood. This varies as a rule with the depth of anesthesia. Ether itself induces histotoxic anoxia.[72] Shaw, Steele and Lamb [73] found ether to decrease the saturation of the arterial blood with an increase of its oxygen capacity. Their findings indicated the existence of anoxic anoxia in subjects under ether anesthesia. The stertorous and labored respirations and the excessive mucus present constitute a mechanical hindrance to the diffusion of oxygen from the inspired anesthetic atmosphere into the blood. This, combined with the presence of fluid in the alveoli, contributes also to anoxic anoxia owing to the delivery of insufficient oxygen to the blood by the lungs.

Postoperatively, the patient showed signs of cerebral oxygen want as described by Waters,[53] indicated by headache, restlessness, delirium and anxiety. Hewitt [74] mentioned that hallucinations may occur in patients who have been subjected to want of oxygen to various degrees. This discussion does not pretend to demonstrate the cause of ether convulsions but rather the part that cerebral oxygen want may have played in the production of convulsions in the patient described. The presence of a strain of streptococci which might have induced sensitiveness to ether has not been ruled out in this case. Oxygen studies were not made but the clinical picture is a sufficient basis for the diagnosis of cerebral oxygen want.

From the foregoing discussion it is plausible that cerebral oxygen want may have developed in this patient at some time during the induction or the maintenance of surgical anesthesia. Careful analysis of the

69. Bastedo, W. A.: Materia Medica, Pharmacology, Therapeutics and Prescription Writing, ed. 4, Philadelphia, W. B. Saunders Company, 1937, p. 510.

70. Embley, E. H.: The Action of Ether upon the Circulation, J. Biochem. **5**:79, 1910.

71. Haldane, J. S.: Symptoms, Causes and Prevention of Anoxemia and the Value of Oxygen in Its Treatment, Brit. M. J. **2**:65 (July 19) 1919.

72. Brow, G. R., and Long, C. N. H.: Biochemical Changes in the Heart Muscle During Anesthesia, Anesth. & Analg. **9**:193 (Jan.-Feb.) 1930.

73. Shaw, J. L.; Steele, B. F., and Lamb, C. A.: Effect of Anesthesia on Blood Oxygen, Arch. Surg. **35**:1 (July) 1937.

74. Hewitt, F. W.: Anaesthetics and Their Administration, ed. 5, London, Oxford University Press, 1922, pp. 120 and 246.

case will show: (1) that this patient had a slight elevation of temperature which increased his oxygen demand; (2) depressing preoperative medication decreased the oxygen saturation of the blood and resulted in anoxia; (3) asphyxia incident to induction of anesthesia with a mixture of nitrous oxide and oxygen produced anoxic anoxia; (4) the mechanical hindrance incident to the stertorous and labored respirations as well as the excessive mucus which was present during the seizure contributed to the anoxia. These factors combine with the anoxia of ether anesthesia to produce the dread clinical picture of ether convulsions.

SUMMARY

A case of ether convulsions in a 14 year old white boy is here recorded.

The etiology of ether convulsions is discussed. No uniformity of opinion concerning the causative factor or factors was found in the literature.

Descriptions of treatment in the literature are indefinite and inconclusive; however, the majority of authors agree that a barbiturate, preferably evipan, should be given.

The choice of anesthesia is debatable, but the spinal, regional and infiltration types seem to be the safest for patients with toxemia.

The factors producing oxygen have been discussed as possible causes of ether convulsions.

Finally, as a solution to the problem has not been found, the anesthetist should be constantly on the alert so that the condition may be recognized early and treatment instituted immediately if this appalling mortality is to be reduced.

LARGE SOLITARY CYSTS OF THE KIDNEY

TYPES, DIFFERENTIAL DIAGNOSIS AND SURGICAL TREATMENT

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No comprehensive clinicoanatomopathologic classification of renal cysts has been published, so far as I have been able to discover. There was formerly much confusion with reference to large solitary serous cyst and polycystic disease of the kidneys, both as to their pathogenesis and as to their clinical manifestations. Especially has there been difficulty in differentiating preoperatively between large serous cyst and hemorrhagic cyst of the kidney and between both of these and neoplastic tumor. Accordingly it seems desirable to present such a classification with a view to promoting a better understanding of these cystic formations, the origin of which has been shrouded in obscurity and the differentiation of which is still attended with so much difficulty. In fact, only since the arrival of modern methods of roentgenographic and urographic examination has it been possible to make a preoperative diagnosis with reasonable assurance and to differentiate large serous cyst of the kidney from solid tumor of this organ or of the neighboring viscera.

I wish to emphasize the feasibility and the importance of recognizing before operation not only the presence of a renal cyst, but also the type of such a cyst and its location, size and nature, as well as the best avenue of approach, since on this recognition must depend the prognosis and the form of operative treatment that is appropriate in each case. In the past most cases of large serous cyst of the kidney were not preoperatively diagnosed; the cyst was usually discovered in the course of laparotomy, naturally to the detriment of the patient, or was diagnosed at autopsy.

Today, the finding of such a cyst is no longer a rarity, and the approach to the cyst by a logical route determined in advance of operation has become surgically possible. On the basis of 10 cases hereinafter reported, I have undertaken to review the principal points to be considered in differential diagnosis and to point out the considerations that must govern the choice of an operation, since the surgical procedure will be conservative or radical, according to the type of case in question.

Read at the thirty-eighth annual meeting of the American Urological Association, Colorado Springs, Colo., May 21, 1941.

It must be emphasized, however, that in most cases the cyst can be treated conservatively. As a rule the sacrifice of a kidney is not necessary or justifiable and is to be considered only in those exceptional cases in which the cyst is associated with complications that render nephrectomy inevitable.

HISTORY AND LITERATURE

The large serous cyst of the kidney has long been known and has been recorded in ancient works on pathology, but no definite account of its clinical history has appeared until relatively recent times. Renal cysts were described by Fabricius of Hilden, known as the Father of Germany Surgery, who died in 1634. In the same century the famous English clinician Thomas Willis made some allusions to cystic formations within the kidney but made no clear differentiation of types. In 1833, Hawkins gave a detailed account of an "encysted serous tumor of the kidney" in a small boy 6 years of age treated in the service of one Dr. Seymour by the administration of "calomel, castor oil, leeches and an ointment consisting of iodine and mercury in equal parts, combined with repeated puncture, notwithstanding which the child died."

Isolated cases of serous or blood cyst of the kidney were reported by Hare (1850), Lancereaux (1858), Thomson (1861), Campbell (1874), Virchow (1869) and Laveran (1876). Virchow suggested that this type was the result of papillary inflammatory obstruction during intrauterine life. In 1874, Campbell did the first successful nephrectomy in such a case. Lancereaux distinguished between serous and hemorrhagic cysts, while Laveran was the first to differentiate large solitary cyst from polycystic disease of the kidney. In 1865 Touren presented a thesis in which he reported several cases of large serous cyst.

Not until 1906 was any comprehensive research done on the subject, when Simon discussed in a thesis 52 cases which he had collected from the literature. In 1911, Brin removed some doubtful cases from among these and replaced them with others more reliable, bringing the number to 53. By 1925, 120 cases had been collected by Laquière; Kretschmer brought the figure to 150 in 1930, and Stirling, in 1931, found 230 cases on record. Finally, in 1932, Simkow, in a thesis, reported on his collection of 315 cases of large serous cyst of the kidney, but many more cases have since been reported, indicating that the condition is not as rare as was formerly believed. Speaking in terms of percentage, Branch stated in 1929 that pathologists see these large renal cysts in from 3 to 5 per cent of routine autopsies.

Within the last two decades the causation and the embryology of these cysts have been investigated by a number of writers, among whom may be especially mentioned Rayer, Le Dentu, Küster, Caulk, Hepler

and Kampmeier. With reference to the difficulties of diagnosis, contributions have been presented by Wulff, Vogel, Fowler, Schulman, Giuliani, Lipskeroff, Cunningham, Chiasserini, Cassioli, Herbst, Higgins, Quinby and others. Modes of treatment have been discussed by Albarran and Imbert, Lejars, Tuffier, Clute, Judd and Simon, Kretschmer, Barney, Colston, Kirwin, O'Conor, Fish and many others.

CLASSIFICATION

As may be seen in table 1, cysts of the kidney fall into three main groups:

The first group consists of the multiple minute cysts commonly found in kidneys of patients with chronic nephritis or even in normal kidneys. These are of no clinical or surgical significance and will not be discussed here.

In the second group are the cysts found in polycystic kidneys, which likewise are not dealt with in this paper. Polycystic disease of the kidney is overwhelmingly bilateral, but in rare instances it has been found to be present in only one of the kidneys, while the other was normal. Polycystic disease of the kidneys, always congenital, may be accompanied by any other type of associated pathologic change and has been discussed exhaustively in the literature by a great many authors.

In the third group are the large solitary serous cysts, which constitute the subject of this paper. Although termed solitary to distinguish them from the cysts of polycystic kidneys, serous cysts may not in fact be single, since it is not uncommon to find one large cyst, outstanding by reason of its size, accompanied by one or several smaller cysts. But, because of the relative insignificance of these smaller sacs and because they do not form groups and do not become fused but remain separated by sound portions of renal parenchyma, the term "solitary" continues to be appropriate. Usually, however, cystic formations of the type in question are now spoken of as "large serous cyst of the kidney," even though the size of the large cyst may not exceed that of a walnut. The finding is usually a large simple cyst, filled with serous fluid which occasionally becomes hemorrhagic, and in some cases it attains a great size, filling the entire abdominal cavity.

With reference to origin, cysts of this type may be divided in general into those that are congenital and those that are acquired. However, as will be seen when the causation is discussed, it is an open question whether there is not in every case an embryonic base for the cyst's development, constituting the soil on which some trauma or other cause acts at a later period to bring the cyst into manifestation from what was previously only a state of potentiality. Nevertheless, from the fact that

in the majority of cases there is no sign of the existence of such a cyst until maturity has been reached, i. e., between the ages of 30 and 70, one is justified in assuming that some of these cysts may properly be classi-

TABLE 1.—*Classification of Cysts of the Kidney*

- Multiple minute cysts of nephritis
- Polycystic kidney disease
- Solitary cysts
  - Congenital
    - Unilateral
    - Bilateral
  - Acquired
    - Unilateral
    - Bilateral
- Large solitary cysts of the kidney
  - According to number
    - Unilocular
    - Bilocular
    - Multilocular
  - According to size
    - Small
    - Large
    - Voluminous
  - According to location
    - Intrarenal
      - Upper pole
      - Lower pole
      - Convex border
    - In anomalous kidney
      - In isthmus of horseshoe kidney
      - In hydronephrosis
      - In aplastic kidney
      - In double kidney
      - In ectopic kidney
    - Perinephric.....
      - Between the two layers of renal capsule
      - Between kidney and its fibrous renal capsule
      - Pararenal pelvic cysts
    - Pararenal.....
      - In embryonic wolffian or müllerian ducts
      - In teratoma
      - In fatty capsule
      - In lymphatic tissue
      - In neurologic tissue
      - In perirenal hematoma from ruptured kidney
    - In other neighboring organs
      - Anterior
      - Posterior
      - At ileum or pyelorenal
      - Adrenal
      - Liver
      - Pancreas
      - Spleen
      - Ovaries
      - Omentum
  - According to type of lesion
    - Serous
    - Hemorrhagic
    - Purulent
    - Containing a tumor
      - Simple thin-walled cyst containing serous fluid and arising from renal parenchyma with no pyelic connection
      - Cyst connected with a calix or with the renal pelvis
      - Extrarenal or pararenal cysts
    - Calcified
    - Hydatid
    - Dermoid
    - Tuberculous

fied as acquired. On the other hand, the finding of such a cyst in an infant a few weeks of age clearly indicates congenital origin.

The number of pockets in the large serous cyst is subject to some variation, for it is found as unilocular, bilocular or multilocular. In all cases the cavity is traversed by walls, complete or incomplete, which may

subdivide it into separate pockets or may leave it with intercommunicating chambers partially separated by septums.

The size of the large serous cyst varies through a wide gamut, running from that of a walnut to that of an orange or grapefruit in the average case but attaining in exceptional cases such voluminous dimensions that the entire abdominal cavity is occupied by the cystic sac, causing the other viscera to be crowded out of their natural position and thereby to suffer great detriment. The cyst may accordingly be known as small, large or voluminous. In 1 of 2 cases in which operation was performed by Kelly, the cyst contained 2,300 cc. of blood-stained fluid; in the other, 1,000 cc. of clear serous fluid.

As to location, the large serous cyst of the kidney may be found at the upper or the lower pole of the kidney, on its convex border, within the kidney parenchyma, on the posterior or the anterior surface, at the internal border or at the hilus (fig. 1 *A*). In Simkow's series the cyst was at the lower pole in 78 cases and at the upper pole in 39; on the anterior surface in 11 and on the posterior in 3. In a case of Hertz the cyst occupied both poles simultaneously. There have been other cases in which the cyst was pyelorenal.

Not infrequently solitary serous cyst is found in an anomalous kidney, as for example, in a horseshoe kidney, in which it has been observed occupying the isthmus, as in Moynihan's case, or in one or the other portion of the double organ. Aplastic kidney, double kidney and ectopic kidney have all been found associated with solitary serous cyst.

A cyst developing at the expense of the kidney may be perinephric, pararenal or even within some other neighboring organ. The perinephric cyst may lie between the two layers of the renal capsule, between the kidney and the fibrous capsule or within the kidney parenchyma close to the renal pelvis but not opening into the latter. The pararenal cyst may be encountered within an embryonic wolffian or müllerian duct, or in a teratoma; it may lie within the fatty capsule of the kidney or within the renal lymphatic tissue, or it may develop in a perirenal hematoma from a ruptured kidney.

The large serous cyst of renal origin may be met with likewise in the adrenal glands, the liver, the pancreas, the spleen, the ovaries, the omentum or other neighboring viscera on which it has encroached in the course of its development. It is present in some cases of hydronephrosis but exists independent of the latter.

A cyst that begins as a simple serous cyst of the kidney may in the course of its development undergo changes that affect its type (fig. 1 *B*). It may thus become a hemorrhagic cyst if rupture of a vessel occurs within its wall; infection may cause it to become a purulent cyst; within

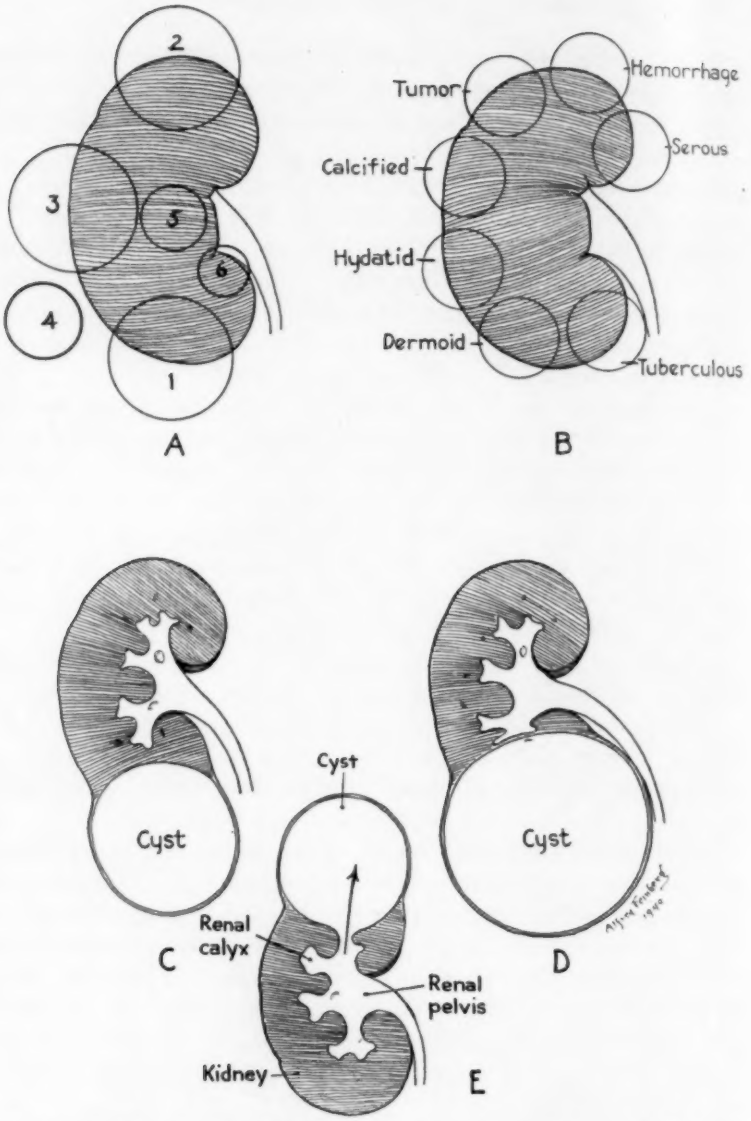

Fig. 1.—Classification and clinical types of large solitary cyst of the kidney. *A* represents the order of frequency with reference to anatomic position: *1*, the lower pole; *2*, the upper pole; *3*, the external border; *4*, pararenal site; *5*, intrarenal site; *6*, pyelorenal site. *B* represents the types most commonly found in order of frequency: large serous cyst, hemorrhagic cyst, cyst containing a tumor, calcified cyst, hydatid cyst, dermoid cyst and tuberculous cyst. *C* illustrates a sagittal view of the kidney with a cyst of the lower pole lying within the parenchyma but having no pyelic connection with the excretory apparatus of the kidney. *D* shows another type, in which there is a larger cyst at the lower pole of the kidney, compressing the lower calix and displacing the ureter but still not opening into either the calix or the renal pelvis. *E* illustrates the large single cyst at the upper pole of the kidney connected with the upper calix.

its contour there may arise a true neoplastic tumor masking the diagnosis; frequently such a cyst may become calcified or may contain a calculus or calculi; more rarely a combination of lesions may be present in the cystic kidney. Hydatid, or echinococcic, dermoid and tuberculous cysts have all been found in the group of serous cysts of the kidney.

When a cyst is within the kidney structure, it may or may not have a connection with a calix or the renal pelvis. Such a connection is rare in a large simple serous cyst of the kidney. Even when the cyst is of considerable size and by compression has destroyed a substantial amount of renal parenchyma, no connection is the rule (figs. 1 *C* and *D*). However, in cases complicated by infection or another type of associated lesion, an opening may develop which can be demonstrated urographically and anatomopathologically (fig. 1 *E*).

PATHOGENESIS

The exact cause of large serous cyst of the kidney is still unknown, although modern modes of investigation have thrown a certain amount of light on it.

Various theories have been set forth, each with some degree of plausibility. Albarran (1903) expressed the opinion that the cyst is the result of a simple variety of polycystic degeneration confined to a restricted portion of a kidney and leaving the rest of the renal parenchyma intact. He thought that a number of smaller cysts became fused together, with production of one cyst of greater or lesser size. He suggested also that since the cyst is lined with epithelium, it might be a neoplasm which has assumed a cystic character. It is now known, however, that this epithelial lining is by no means a constant finding and that when it exists it does not appear to possess any special significance.

Virchow thought the cyst was due to interstitial nephritis in intrauterine life leading to inflammatory sclerosis and consequent occlusion of some of the uriniferous tubules with resultant formation of a retention cyst.

The theory that the cyst has its origin in an embryonic rest and developmental defect has found many adherents. A failure of the S-shaped anlagen of the uriniferous tubules to unite with the straight collecting ducts owing to some obstruction from within or without has been generally accepted. Some have held that the cyst is due to rupture of the uriniferous tubules and shedding of epithelial cells into the intercanalicular connective tissue. Rokitansky thought that it is formed by metamorphosis of the cells of the malpighian bodies. Stoppage of the canals with salts or other debris after a localized inflammatory process has obliterated a segment of the tubule or the duct has been another common hypothesis.

In 1923, Kampmeier, in an actual study of fetuses, observed the apparently constant appearance of renal cysts at a certain period of fetal life, about the end of the third or the beginning of the fourth month. He noted that normally these redundant structures degenerate but pointed out that if they fail to do so at the end of the allotted time and instead continue to grow and expand, to the detriment of other adjacent normal structures, a normal physiologic event is converted into an abnormal or pathologic condition. He considers it reasonable to assume that the renal cyst is more frequently produced by the persistence and later expansion of cystic tubules which failed to collapse during fetal life than by an occlusive process in the embryo.

In 1930, Hepler succeeded in producing renal cysts in rabbits. He noted that simple occlusion does not result in cyst formation but that there must be in addition interference with the local blood supply. He found that group tubular obstruction plus anemic degeneration causes a cyst to form. He observed the development of obliterating endarteritis with sclerosis of groups of arterioles and glomeruli resulting in nutritional disturbances of the adjoining parenchyma; the subtending tubules then atrophied with substitution of connective tissue, whereat small groups of tubules, the glomeruli of which were not involved, became occluded by peritubular sclerosis and this led to dilatation with cysts. Although the cysts were small, Hepler expressed the opinion that if larger vessels are occluded, large cysts must form. The relation of some of Hepler's experimental cysts to nephritis is undeniable; in 28 animals there were definite nephritic changes, chiefly of a vascular nature.

Caulk, who discussed the pathogenesis of the large serous cyst of the kidney at some length, held that the weight of evidence is on the side of congenital origin but that some form of obstruction in the uriniferous tubules always plays a part and causes retention. It is evident that in many cases trauma or some other acquired pathologic condition later brings the cyst into manifestation. Thus it has been pointed out that the cyst appears most frequently at the age when arteriosclerosis has set in. It seems that it grows slowly in the early period of life but that it is related in some way to the acquired renal lesions of adult life, which start it and stimulate it to rapid growth in the middle and later years of life. The most common form of obstruction is localized inflammation with peritubular sclerosis and contraction leading to retention.

It has not escaped notice that congenital renal anomalies are frequently the site of cystic formations. Cyst associated with supernumerary kidney, congenital solitary kidney, ectopic kidney and horseshoe kidney have all been reported as not infrequent.

Haslinger thought that in view of the widely different localizations of the large serous cyst of the kidney it must be concluded that the

pathogenesis is not the same in all cases. Pousson shared this view and expressed the belief that the cyst arises from multiple causes and cannot be attributed to any single uniform origin. At all events, it seems certain that both congenital and acquired factors are at work in most of the cases.

SYMPTOMATOLOGY

In most cases, solitary cyst of the kidney gives no symptoms until the cyst attains a sufficient size to exert pressure on other abdominal organs. It is especially worthy of note that urinary symptoms are commonly absent for a long time. The most that the patient feels is a vague sense of fulness in the abdomen or of heaviness on the side chiefly affected. As the cyst continues to grow, there may be pain in the costovertebral angle or in the lumbar or the lower dorsal region. The pain may be indefinite and dull, or there may be attacks of more or less acute distress, which subside only to return at a later time. The pains may radiate into the lower extremities, the ureter or the testis. Laquière's patient had such acute pains in her back that constant administration of morphine was necessary, and the pains were of such a nature that a diagnosis of Pott's disease was made. Hofer had a case in which the pressure of the cyst occluded the common bile duct and also caused anuria. When the cyst is at the upper pole of the right kidney the renal symptoms are often masked by those of the liver and the gallbladder. Gastrointestinal symptoms are frequently the dominant manifestations and may be the only ones. Nausea, vomiting and even intermittent occlusion of the descending colon may be present. Since the cyst, except in rare cases, does not open into the renal pelvis or calices but remains outside of the excretory system of the kidney, it is usual to find no symptoms referable to that organ; this accounts for the infrequency with which the correct diagnosis has been made in the past before the use of pyelography and roentgenography was general. However, when the cyst is large or appropriately located, it may compress the urinary passages and cause symptoms within the urinary system. Hydronephrosis and pyonephrosis due to such compression of the ureter have frequently been observed. Hematuria with no other assignable cause than a serous cyst is not infrequent. Renal ptosis is present in a substantial number of cases. More frequently, however, these cysts do not suggest a renal origin; cystoscopy reveals nothing, and renal functional tests and catheterization show an unimpaired kidney and renal pelvis. On palpation, however, a fluctuant mass with smooth contour may be felt beneath the anterior wall of the abdomen projecting toward the ribs and dull to percussion. The mass is insensitive to pressure and exhibits a striking mobility, especially when renal ptosis is present and the mass is at the lower pole or external border of the kidney.

According, then, to the location and the size of the cyst, the symptoms will vary with the case, producing in extreme development weakness, secondary anemia and emaciation, with profound repercussion on the general state of health. If the cyst is in the upper pole of the kidney and if its size and weight are considerable, it will push the kidney downward and may give rise to the entire gamut of symptoms observed in cases of nephroptosis or in an ordinary case of renal tumor, pyelitis or pyelonephritis. If hemorrhage occurs or if infection is superimposed, the systemic symptoms will be severe. Smaller cysts, however, may give no symptoms whatever and may be discovered only by accident at roentgen examination or at autopsy.

PATHOLOGY

Unlike polycystic disease of the kidneys, the presence of a large serous cyst within the renal organ is usually unilateral, with the other kidney normal. Opinions differ as to whether the cyst takes its origin from the cortical or the medullary substance. Regardless of origin, however, it involves the cortex. A cyst at the upper pole will be more likely to produce pressure changes, dragging the kidney down and compressing the ureter, resulting in pyelectasis. A cyst in the lower pole, on the other hand, frequently produces hydronephrosis. According to Terrier, in 6 out of 7 cases the cyst is at the upper pole, and in 1 in 7, at the lower. Simon, however, with a series of 52 cases, found the cyst at the lower pole in 18 cases and at the upper in only 8; in other cases it was in various parts of the organ. The size, as already mentioned, is variable, but most frequently it is about that of an orange. In many cases in which the cyst cannot be removed, the size can be estimated only by the amount of fluid it contains, which in extreme cases may reach as much as 16 liters (case of Goenczy). The shape is spheroid or ovoid, and the contour is smooth.

As the cyst increases in size, it displaces the renal parenchyma, in which it digs, as it were, a bed for itself; it creates a corresponding depression in the parenchyma, which thereby tends to become more or less atrophied for a certain depth, below which it remains normal. Where the cyst encroaches on the parenchyma, slight chronic inflammation may be met with fatty infiltration, also slight, in the uriniferous tubules. Otherwise the kidney itself remains normal in uncomplicated cases.

The wall of the cyst is thin, fibrous and transparent; its color is whitish blue or yellowish, according to its content. It is traversed by a great number of vessels, the rupture of any one of which may cause the content of the cyst to present a hemorrhagic appearance. The thinness of the wall of the serous cyst, however, distinguishes it from the true hemorrhagic cyst, the walls of which exhibit a great thickness.

The wall is composed of three layers, the outermost of which is the fibrous capsule of the kidney; the median is of connective tissue, in which are vessels and remnants of atrophic glomeruli and uriniferous tubules, with a few elastic fibers; the innermost is of pavement or cuboid epithelium, usually smooth but sometimes containing remains of trabeculae and septums. The wall, however, is subject to considerable variation; sometimes it consists of only two layers without epithelium, or, again, it has several layers of epithelium, in some places even hornified. Calcareous salts may be found within the wall at times.

The content of the cyst is a serous fluid (sometimes serohematic), usually straw or amber colored; it may be clear or turbid or sometimes even gelatinous. Its specific gravity varies from 1.002 to 1.018. Its chemical composition, however, is rather constant; it consists of water, albumin, chlorides, phosphates, sulphates, serum, globulin, fats, cholesterin crystals and urea. The presence of urea has been the subject of some controversy, some authors contending that no element of the urine is ever present. The consensus, however, is that urea is commonly present, though in minute quantities. There are also found epithelial cells, lymphocytes, leukocytes and a few red blood cells.

As the cyst grows, it forms adhesions to the walls of other nearby organs, such as the spleen, the pancreas, the ascending and the transverse colon, the lower surface of the liver, the duodenum and even the stomach. In cases in which it attains a great size, it may also adhere to the abdominal wall at various points, or to the diaphragm if the cyst is located at the upper pole. As a rule it is sessile and in most intimate relation to the renal parenchyma, from which its enucleation is difficult and sometimes impossible. In rare cases, however, a pedicle connecting it with the upper pole or with the hilus is present; in these cases the cyst causes extrarenal pressure on the pelvis of the kidney.

In the typical uncomplicated cyst, there is no communication with the renal pelvis or calices. There are cases, however, in which an opening into a calix develops from infection or other cause (as for example in cases of echinococcic cysts); this at once causes a change in the clinical picture, since now the content of the cyst and the urine within the renal pelvis inevitably mingle, and complications arise. Occasionally a cyst wall thinned to the point of rupture may break through into any neighboring hollow organ against which it has been forcibly pressed in its growth. According to the type of lesion or fluid found in the renal cyst, the latter may belong to any one of the different types of cyst established in the clinicoanatomopathologic classification presented in this paper. Finally, it is not unusual to find reported in the literature hemorrhagic serous cyst associated with renal neoplasm: adenocarcinoma (Scholl), carcinoma (Le Comte), sarcoma (Crabtree), Wilms's tumor (Neff), hemangioma (Begg), hypernephroma (Cun-

ningham), papillary cystadenoma (Colston). Bockenheimer, Moynihan, and Judd and Simon reported cases in which the cyst was associated with horseshoe kidney; Fowler described a case in which there were anomalies of the renal blood vessels. In my own series, there is 1 case of the bifid type of renal pelvis, and another 1 in which the nephrectomized specimen removed at operation revealed the presence of a malignant Wilms tumor attached to the bottom of the renal cyst.

DIAGNOSIS

As recently as 1925, Laquière stated that in only 11 cases had a positive diagnosis of solitary cyst of the kidney been made preoperatively among 121 cases that he had been able to collect from the literature. Since the presence of a cyst is not revealed by any modification of the urine and since the functional capacity of the affected kidney is sometimes actually better than that of the other kidney, the existence of such a cyst has seldom been recognized before operation and the demonstration of it has constituted one of the most difficult problems. In 1932, Simkow brought the number of cases in which preoperative diagnoses were made up to 33 in his total collection of 315 cases.

This failure to recognize the condition has been due to the fact that in the vast majority of cases there is no communication between the cyst and the renal pelvis, and the cyst, being in the cortex, thus remains a thing apart from the urinary system (fig. 2 *A, B* and *C*). The patient will ordinarily first consult a general practitioner for symptoms unrelated to the urinary tract and will be examined for troubles in the gastrointestinal organs; the result of this has been that not a few laparotomies have been performed on the basis of a wrong diagnosis. As a rule the patient does not reach the urologist until the cyst has attained considerable size, causing it to exert pressure on the urinary passages and thus to attract attention to a possible abnormality in this region.

The history and the subjective symptoms of the patient will therefore throw little light on the diagnosis since they are identical with those of other conditions in which there is compression and obstruction in the urinary excretory tract. The patient reaches the urologist only when objective symptoms occur, such as painless hematuria, frequency of urination, dysuria or pyuria. Physical examination may then reveal the presence of an enlarged palpable kidney and sometimes of an elastic tumorous mass on palpation of one or the other side of the abdomen. However, there is so little characteristic about this that it is impossible to say to what organ it belongs or whether it is a cyst or a neoplasm, and if the cyst is in the upper pole of the kidney it may not be palpable at all. The composition of the blood will ordinarily be normal.

Cystoscopy will show nothing characteristic that might not be observed in various diseases of the urinary tract. Catheterization of the ureters may confirm the evidence of obstruction on one side, and in the presence of a palpable mass, usually painless, may direct the diagnosis toward that of tumor but will not reveal whether the mass is within the kidney or is making pressure from outside that organ; nor will it disclose the nature of the tumor mass.

Roentgenography, intravenous urography and retrograde pyelography, then, constitute the principal means of recognizing large serous cyst of the kidney. In the pyelogram, if the cyst is of sufficient size to bulge into the renal pelvis or a calix, a filling defect will be seen producing a deformity of that cavity.

In the great majority of cases the pyelogram will be normal if the cyst is relatively small and does not encroach on the calices or the renal pelvis. If, however, a small cyst is growing close to a calix or the renal pelvis and is so located as to exert pressure, the pyelogram will reveal this fact. This is shown in 3 of my cases hereinafter reported.

When the cyst is at the lower pole, it is so likely to cause hydronephrosis that any slight flattening which the pressure of the cyst itself may make on the pelvis is likely to be masked by the shadow of the hydronephrotic sac. In cases in which the cyst is large enough to displace the ureter, cause obstruction and interfere with drainage, it is likely to betray its presence also when other means of examination are employed.

Compression of the calix that lies nearest to the cyst is highly suggestive of the presence of a solitary renal cyst. One or more calices may be shortened, blunted or in some instances wholly obliterated. As pressure increases with the growth of the cyst, the pyelogram reveals retraction, flattening or elongation of calices that were previously normal. For this reason it is desirable to repeat the making of pyelograms from time to time when the existence of a cyst is suspected. In cases in which the cyst arises not from either pole but on the mesial border of the kidney, the calices remain normal, but the adjacent portion of the pelvis itself becomes flattened under the compressive action of the cyst.

In many cases in which the patient is properly prepared, the outline of the cyst can be clearly made out in a roentgenogram, especially of a cyst in the lower pole. The margin of the cyst will be continuous with the kidney, but a difference will be observable between the density of the cyst and that of the renal organ. The ureter will frequently show displacement at the same time. The cyst is recognizable by its smooth round shadow, which contrasts in contour and density with the shadow of the kidney and the other adjacent organs. Since the fluid within the serous cyst is nearly transparent, the line of the psoas muscle can be readily visualized through it, especially when the cyst is at the lower pole; this would not be possible if the tumor mass were a solid neoplasm.

When the cyst is at the upper pole, the diagnosis is much more difficult and is most frequently impossible. In such cases the weight of the cyst forces the kidney downward, resulting in ectopy of the organ, which may be recognizable in a roentgenogram. Pressure applied on the cystic mass, when this is palpable, was found by Ormond to move the renal pelvis downward to a sufficient extent to show in a pyelogram; a difference was observable between pyelograms made before and after the application of such downward pressure.

According to Quinby and Bright, the diagnosis of cyst at the upper pole of the right kidney has seldom been made preoperatively; this was accomplished in only 5 of 30 reported cases. Such a cyst is easily mistaken for a tumor of the gallbladder or some other pathologic condition in the liver. When a pyelogram is made, it may be possible to diagnose a tumor of the kidney but not to make the differentiation between a neoplasm and a benign cyst in advance of operation. According to these authors, pyelography gives the best information, having shown deformities or displacement of the upper calices in 75 per cent of the 36 cases they analyzed in which the upper pole was the site of the cyst.

Renal arteriography, needle aspiration of the cyst and injection of air into the cyst as a contrast medium, particularly after the fluid of the cyst has been aspirated, are methods of diagnosis which have been used and which may be recommended in certain difficult cases, although in my series the cyst was aspirated in only 1 case for the purpose of diagnosis and treatment, in order to note whether it was refilled a short time afterward, as commonly happens after the aspiration of the fluid in hydrocele of the tunica vaginalis.

In summary, the urographic evidences of a large solitary cyst of the kidney may be as follows: (1) compression of the renal pelvis or of one or more calices; (2) changes in the position of the axis of the kidney; (3) inward displacement of the ureter; (4) displacement or rotation of the renal pelvis upward or downward; (5) visualization of the shadow of the cyst; (6) crescent shape of the renal pelvis or of a calix; (7) calcification of the cyst walls in some cases; (8) visibility of the psoas muscle through the walls of the cyst; (9) shadow of the cyst superimposed on the kidney shadow; (10) visualization of the cyst furnished by pyelovenous backflow.

In a pyelogram solid tumor of the kidney as a rule shows more marked invasion of the calices and the renal pelvis, since the growth of the tumor extends inward to occupy the renal parenchyma, while the cyst tends to spread outward. The pyelogram of the tumor is more disorganized and more bizarre and follows no such rule of uniformity as does that of large simple cyst of the kidney. Further, in cases of

renal cyst the shadow of the kidney itself is usually not enlarged, while a malignant tumor of the kidney causes considerable increase in the size of the shadow.

However, there are cases in which the differential diagnosis of large serous cyst of the kidney is not complete without proper surgical exploration of the cyst, particularly when the patient has a history of hematuria. Such exploration cannot be dispensed with in doubtful cases since to overlook the presence of an associated lesion concealed within the cyst or the kidney, such as malignant tumor, may be more serious and of greater clinical significance for the final prognosis than the apparently benign cyst itself.

Sometimes when the differential diagnosis of cyst of the kidney is doubtful, the repetition of pyelographic studies furnishes a sound criterion. In fact, retrograde pyelograms should be taken with the patient in both the Trendelenburg and the erect position; lateral pyelograms also should be taken whenever indicated, since, as happened in 1 of my cases hereinafter reported, one of the calices may communicate with the renal cyst; when this occurs the pouch or sac of the cyst may be faintly delineated in one of the good films of the pyelogram, and this will serve to clarify the diagnosis.

REPORT OF CASES

CASE 1.—*A woman complaining of pain in the right upper quadrant of the abdomen radiating to the right lumbar region of over eight years' duration had twice been operated on elsewhere—first, ten years previously for chronic appendicitis and again eight years later for a cyst in the right ovary, both times without relief. Urographic studies revealed nephroptosis on the right with a kink of the right ureter, for which she refused operation. After several years of palliative treatment, she finally consented to operation for the condition in the right kidney. At operation a moderate-sized renal cyst attached to the upper pole of the right kidney was found. The cyst was resected, nephropexy was accomplished, and a cure was effected.*

Mrs. M. J. A., a housewife 32 years of age, was referred on Feb. 8, 1934, complaining of pain in the right upper quadrant of the abdomen radiating to the right lumbar region of ten years' duration. She had also slight frequency of urination with dysuria and nocturia. The patient had been married for ten years but had no children, although her menstrual periods were regular. About ten years previously she had been operated on elsewhere for chronic appendicitis and again two years before my examination for removal of an ovarian cyst, but the persistent pain in the right upper quadrant continued to "nag her off and on" without relief. She had roentgen examinations of the gastrointestinal tract and the gallbladder elsewhere, but no definite diagnosis was made. On physical examination the two scars of previous operations were observed in the lower part of the abdomen. The right kidney was low in position, somewhat enlarged, tender and easily palpable; the left kidney was not palpable. Urinalysis showed the presence of a few pus

and red blood cells, albumin and bacteria. The blood pressure was 100 systolic and 60 diastolic. The patient was ill, thin, nervous and anemic. Cystoscopic examination with catheterization of the ureters and differential renal functional test revealed that both kidneys had good urea excretion and phthalein elimination. Microscopic examination revealed pus cells and blood cells in the specimen catheterized from each kidney. Roentgenograms were taken with catheters and instru-

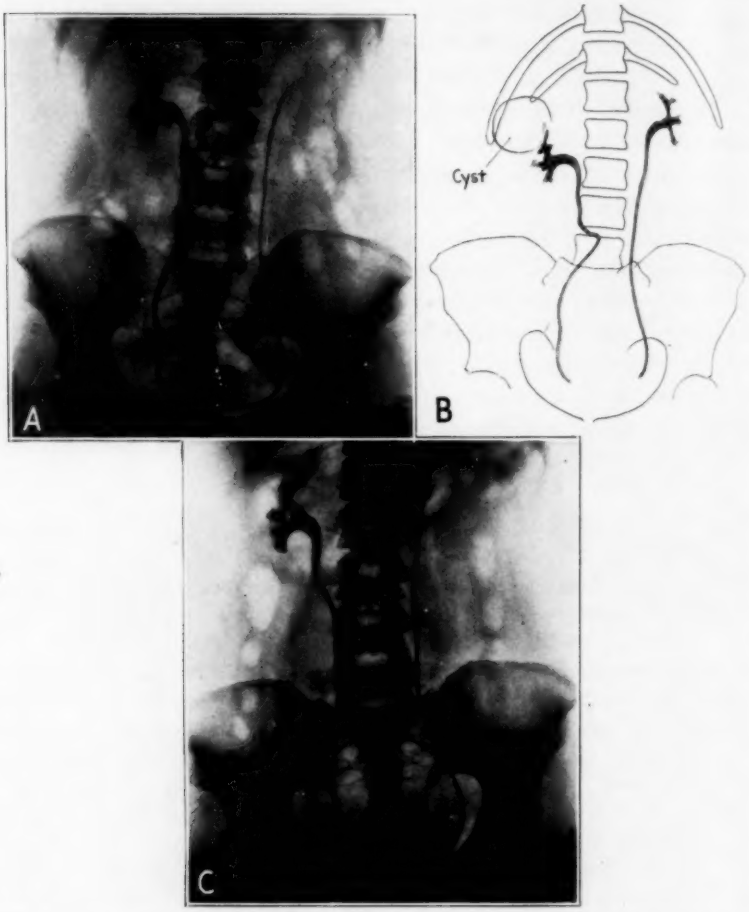

Fig. 2 (case 1).—Pyeloureterograms taken before and after operation; the diagnosis of large serous cyst was made at operation: *A*, right pyeloureterogram showing marked nephroptosis and kink of the ureter; there is a barely visible suggestion of a cyst at the upper pole. *B*, drawing from bilateral pyelogram showing the anatomic position of the cyst found at operation in the upper pole of the right kidney. *C*, right pyeloureterogram one year later. Note the restoration of the right kidney and the ureter to normal position.

ment in position; retrograde pyelograms and pyeloureterograms also were made. These disclosed the presence of nephroptosis on the right, a kink in the right ureter and narrowing of the ureter with evidence of pyelitis and pyelonephritis (fig. 2*A*).

For this condition the patient received a short course of cystoscopic treatments with dilations of the ureter and lavage of the renal pelvis. She was given a low protein diet, forced to take fluids and treated with urinary antiseptics. After she had been seen by a gynecologist and given treatments for sterility, the patient was again sent to me five years later, on Feb. 2, 1939, complaining of persistent dragging pain in the right upper quadrant and the right lumbar region, definitely localized in the right kidney. Nephropexy was again advised. The patient finally accepted operation and entered the Murray Hill Hospital on Feb. 14, 1939, where an operation on the right kidney was performed. A cyst about the size of an orange was found occupying the upper pole of the kidney and plastered by adhesions to the parietal layers of the peritoneum (fig. 2*B*). The kidney with the cyst was freely mobilized by nephrolysis and ureterolysis, then the cyst was clamped, the fluid was aspirated, and the sac was resected (fig. 9*I*). Interrupted sutures were placed at the edge of the cystic sac and that of the proper capsule of the kidney, after which nephropexy was accomplished by fixing the upper pole to the eleventh intercostal space, and the wound was closed in the usual manner, a small cigaret drain being left at its upper angle. The patient had an uneventful convalescence, and the wound healed by primary union. The aspirated fluid was amber in color, and the cyst did not appear to be connected with the upper calix or the renal pelvis. The patient was seen in the office one month later with the wound firmly healed, and she felt happy about the results obtained. One year later she came back at my request for a complete check-up. At that time she was again examined cystoscopically. Renal function from both kidneys was found to be normal. Retrograde pyelograms disclosed that the kidney operated on was in a perfectly normal position and exhibited good drainage as the result of the resection of the renal cyst in the upper pole and the nephropexy (fig. 2*C*). The patient seemed to have recovered fully, since she stated that she had gained more than 30 pounds (13.6 Kg.), felt comfortable and was free from symptoms.

While the result of the resection of the renal cyst followed by nephropexy has been highly gratifying in this case, it must be admitted that the diagnosis of the cyst was made only at the time of operation, owing to the difficulty of preoperative diagnosis of the early renal cyst.

CASE 2.—*A man suffering from hypertension had an attack of painless hematuria of four days' duration, for which he had been examined elsewhere and a diagnosis of tumor in the left kidney made. At the time of my urologic and urographic examination, I diagnosed a solitary cyst at the upper pole of the left kidney; this was confirmed at operation. Partial nephrectomy was planned for removal of the large renal cyst attached to the upper pole of the kidney, but at operation such an enormous cyst was found (it had destroyed more than half the parenchyma and seriously compromised the blood supply of the kidney) that total nephrectomy was carried out with curative results.*

Mr. F. R. V., 60 years of age, was referred for examination on July 6, 1939. He had a history of having had an attack of painless hematuria in December 1938 of four days' duration; complete urographic examination had been carried out elsewhere and a diagnosis of tumor of the left kidney made. He gave a history of having received treatment for high blood pressure; at the time of examination the blood pressure was 250 systolic and 150 diastolic. On physical examination, the patient was observed to be well built but decidedly nervous, emaciated and anemic. The abdomen was distended; the kidneys were not palpable. Rectal

examination disclosed slight enlargement of a leathery prostate. The urethra was permeable to sound F. 25. There was about ½ ounce (14.8 cc.) of residual urine in the bladder. On the left there was evidence of a hydrocele of moderate size. The patient stated that roentgen examination of the gastrointestinal tract and the gallbladder had revealed no abnormalities. Urinalysis showed the presence of blood and pus cells with clumps as well as albumin and innumerable bacteria, streptococci and staphylococci, which persisted in many urinary reports. Chemical examination of the blood revealed the nonprotein nitrogen to be 42.86 mg. per hundred cubic centimeters, indicating marked urea retention; creatinine was 2.2 mg. A blood count disclosed secondary anemia. The patient was examined cystoscopically on July 11, 1939, when plain roentgenograms and bilateral retrograde pyelograms were taken. The kidney function was slightly diminished on the left side compared with the

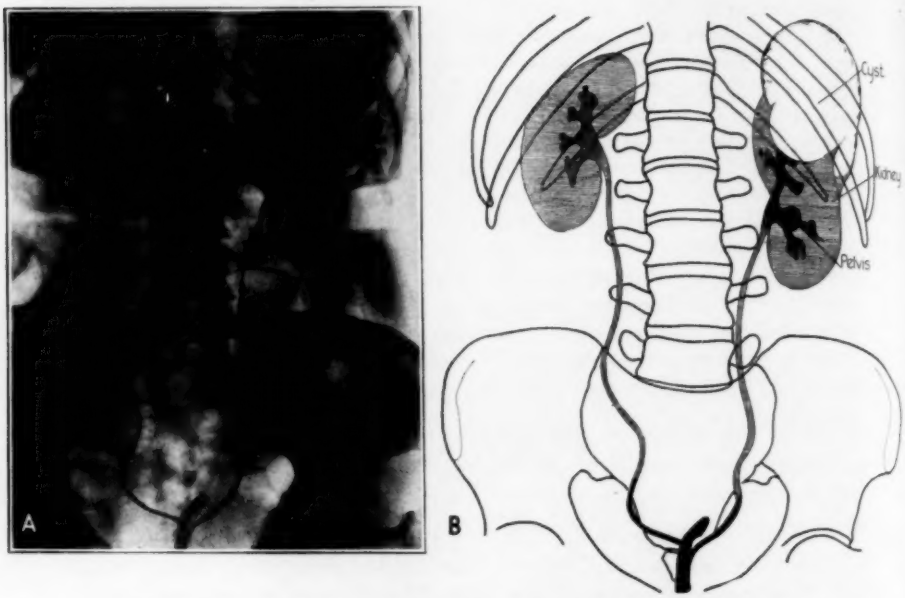

Fig. 3 (case 2).—In this and the following figure are shown various pictures of a large solitary cyst in the left kidney of a man 60 years of age for whom a diagnosis of left renal neoplasm had been made but in whom urographic examination disclosed the presence of a large solitary serous cyst of the left kidney, a diagnosis confirmed at operation. *A*, left pyeloureterogram showing a renal pelvis of the bifid type with definite flattening of the upper calix and a faint outlining of the cyst at the upper pole of the left kidney; revealing also a slight pyelovenous backflow with evidence that the opaque substance has entered the lymphatics surrounding the renal pelvis. *B*, drawing from bilateral pyeloureterograms indicating the actual size and position of the cyst in the upper pole of the left kidney which was diagnosed before operation.

right as to both urea estimation and phthalein elimination. One of the pyelograms disclosed that the opaque substance had spread beyond the upper calix of the left kidney, showing a round shadow which gave the impression of a large solitary

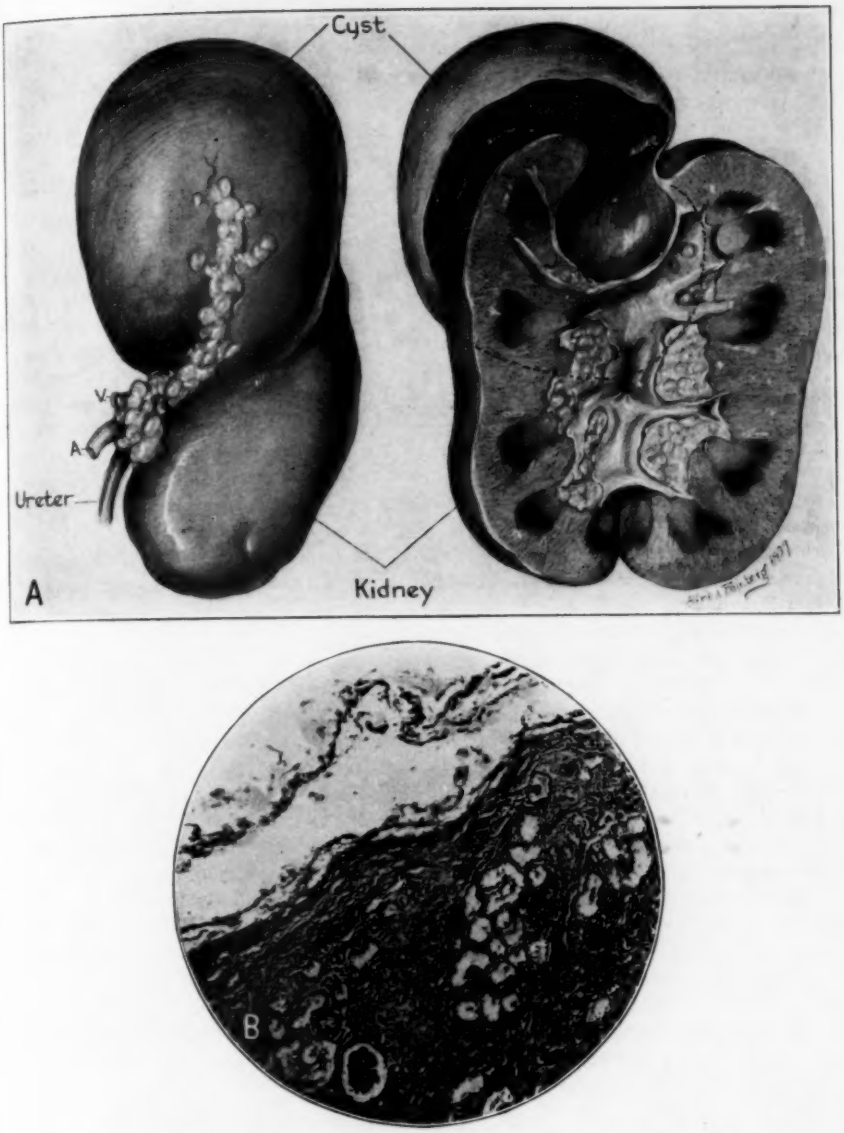

Fig. 4 (case 2).—*A*, drawing of the specimen removed at operation, consisting of the left kidney and the large serous cyst attached to the upper pole. Two views are seen: one showing the appearance before opening; the other revealing the relation of the cyst to the kidney as seen after opening. The cyst extended down the posterior aspect of the kidney almost to the middle of the organ, but had no communication with the renal pelvis. The entire mass of the kidney with its cyst was removed by nephrectomy with gratifying results. *B*, photomicrograph of the histologic section made from the specimen removed at operation showing how the fibrous connective tissue of the cyst wall has encroached on the fairly normal renal parenchyma, which exhibits merely slight atrophy in the kidney substance directly in apposition with the cyst wall, due to the compression exerted by this benign cystic mass.

renal cyst attached to the upper pole (fig. 3 *A* and *B*). The left pelvis was bifid in type, and there was a slight degree of pyelovenous backflow. A diagnosis of large solitary cyst of the left kidney with bifid left renal pelvis was made. The patient was admitted to Doctors Hospital on July 13, 1939 and was prepared for operation on the left kidney. He received daily intravenous infusions and three blood transfusions. After two weeks all the tests were repeated and revealed a definite improvement. Nephrectomy on the left was carried out on July 25, 1939 with the patient under anesthesia induced with cyclopropane. The kidney was exposed in the usual manner by incision in the left lumbar region. When the fatty capsule was opened, the large cyst was found attached to the upper pole of the kidney and extending far down on the posterior surface. Resection in order to save the kidney was at first considered, but owing to the anomalous blood supply of the organ and the fact that the line of demarcation of the cyst extended posteriorly down to the renal pelvis and also in view of technical difficulties with the pedicle for the remaining portion of the kidney, it was decided instead to clamp the pedicle and accomplish nephrectomy. A cigaret drain was left in the upper angle of the wound, which was closed in the usual manner. Convalescence was uneventful. The patient left the hospital on Aug. 14, 1939 with the wound almost closed except for a small sinus in the upper angle, which after several dressings and proper care finally healed. He had gained in weight, and his general health was considerably improved. There was a drop in blood pressure to 160 systolic and 90 diastolic after nephrectomy.

Histologic examination of the specimen removed at operation was made by Dr. H. R. Muller at Doctor's Hospital and disclosed the following information: The kidney was slightly enlarged owing to the presence in the upper pole of a cyst 8 or 9 cm. in diameter. This cyst had a thin fibrous wall and replaced a large portion of kidney substance. It contained clear liquid. It was close to the upper portion of the pelvis but did not actually communicate with the pelvis (fig. 4 *A*). The pelvis had two parts, draining respectively the upper and the lower pole, but these united and had a common ureteral outlet. The cortex and the medulla had normal markings, and the capsule stripped off easily, leaving a smooth surface. The wall of the cyst was composed of fibrous connective tissue in which there were foci of round cell inflammation. It became fused and was continuous with the capsule of the kidney where they met. Glomeruli, tubules of both the cortex and the medulla and blood vessels became involved in the capsule and showed atrophy in the narrow zone of kidney substance directly in apposition with the cyst wall (fig. 4 *B*). These structures being gradually drawn into the wall of the capsule showed progressive enlargement and encroachment on the kidney substance.

Pathologic Diagnosis.—The patient had a benign cyst of the kidney with chronic productive and exudative inflammation in the wall. There were atrophy of the adjacent kidney substance and a double pelvis of the kidney.

This case serves to illustrate the favorable and definitely good prognosis that exists when one is dealing with what proves to be a large solitary cyst of the kidney and not a renal neoplasm. It also shows that notwithstanding the advantage of achieving a urographic diagnosis previous to operation, the urologist must choose at operation the type of procedure that then proves most suitable for the individual patient. It also serves to emphasize that while a conservative procedure of

resecting the cyst may save a properly functioning kidney, it is wiser, when an anomalous blood supply is found in the pedicle and the kidney cannot be saved, to carry out nephrectomy in order to obtain permanent cure.

CASE 3.—*A young woman had suffered from persistent pain in the right lumbar region since the age of 12; ten years later the pain became aggravated. She lost weight and suffered from gastrointestinal disorders. Urographic examination disclosed marked nephroptosis on the right with inward rotation and compression of the lower calix and the renal pelvis. At the time of operation, a cyst of moderate size was found attached to the lower pole of the right kidney. In view of the fact that compression by the cyst had destroyed a great part of the renal parenchyma and also because of the anomalous blood supply of the kidney, nephrectomy was carried out with gratifying results.*

Miss J. M. A., 24 years of age, was examined on Aug. 20, 1940 by Dr. J. P. Lopez of Habana, Cuba, through whose courtesy I am reporting this case in detail. She complained chiefly of pain in the right lumbar region radiating to the bladder region, of several years' duration. She was thin and anemic and suffered from gastrointestinal disorders and slight frequency of urination, dysuria, microscopic pyuria and hematuria. On physical examination, the right kidney was palpable, tender and low in position. A round mass about the size of an orange could be felt attached to the lower pole of the kidney. The left kidney was not palpable. The patient had been examined on several previous occasions and the diagnosis of floating kidney made. Cystoscopy disclosed normal ureteral orifices and a normal bladder. Both ureters were catheterized. The specimen collected from the right kidney was hazy and contained 19 per cent pus cells per microscopic field and Bacillus coli; the urea content was 8 Gm. per liter. The specimen from the left kidney had only 2 or 3 pus cells and 13 Gm. of urea per liter. Indigo carmine appeared in fifteen minutes from the right kidney and in five minutes from the left. A phenolsulfonphthalein test done at another sitting disclosed 22 per cent elimination from the right kidney and 34 per cent from the left; this showed that the function of the right kidney was diminished. A roentgenogram and plain films taken with catheters and instrument in position revealed that the right ureteral catheter was deviated toward the spinal column. Retrograde pyelograms disclosed evidence of slight hydronephrosis with some inward rotation of the entire pelvis. The two lower calices were compressed, and there was also a marked degree of nephroptosis (fig. 5). The left pyeloureterogram was entirely normal. The blood composition, blood count and blood pressure were almost within normal limits. After a diagnosis of right nephroptosis and possible tumor or cyst of the lower pole of the right kidney, operation was performed with the patient under general anesthesia. The kidney was exposed in the usual manner by incision in the lumbar region. A large serous cyst attached to the lower pole was readily seen. It was so deeply situated within the renal parenchyma that almost half of the organ was destroyed by the pressure. Since the kidney could not be saved owing to the anomalous blood supply in the pedicle and evidence of atrophy and diminished function, the pedicle was clamped and nephrectomy carried out in the usual manner. The results obtained were excellent. The specimen removed at operation showed a certain degree of atrophy of the renal parenchyma and the presence of pyelonephritis; it also could be seen that the sac of the cyst had not communicated with the lower calices, to which the cyst was firmly attached.

This case illustrates that when rotation downward and inward with compression of calices and the adjoining pelvis is demonstrated, a diagnosis of large solitary serous cyst of the kidney is warranted in most instances. If the diagnosis had been made early enough, it is possible that heminephrectomy or simple resection of the cyst followed by nephropexy might have saved the organ. However, nephrectomy was

Fig. 5 (case 3).—Bilateral pyeloureterogram showing a large solitary serous cyst of the lower pole of the right kidney in a woman with marked nephroptosis. The cystic condition was diagnosed at the time of operation. The picture discloses a normal kidney on the left side and marked nephroptosis on the right with downward and inward rotation of the major and the minor calices and inward compression of the right ureter by a faint rounded mass in the lower pole of the right kidney (indicated by arrows) which shows evidence also of pyelitis and pyelonephritis. At the time of planned right nephropexy a large solitary cyst of the lower part of the right kidney was disclosed; in view of the fact of an anomalous blood supply, nephrectomy was carried out and resulted in cure.

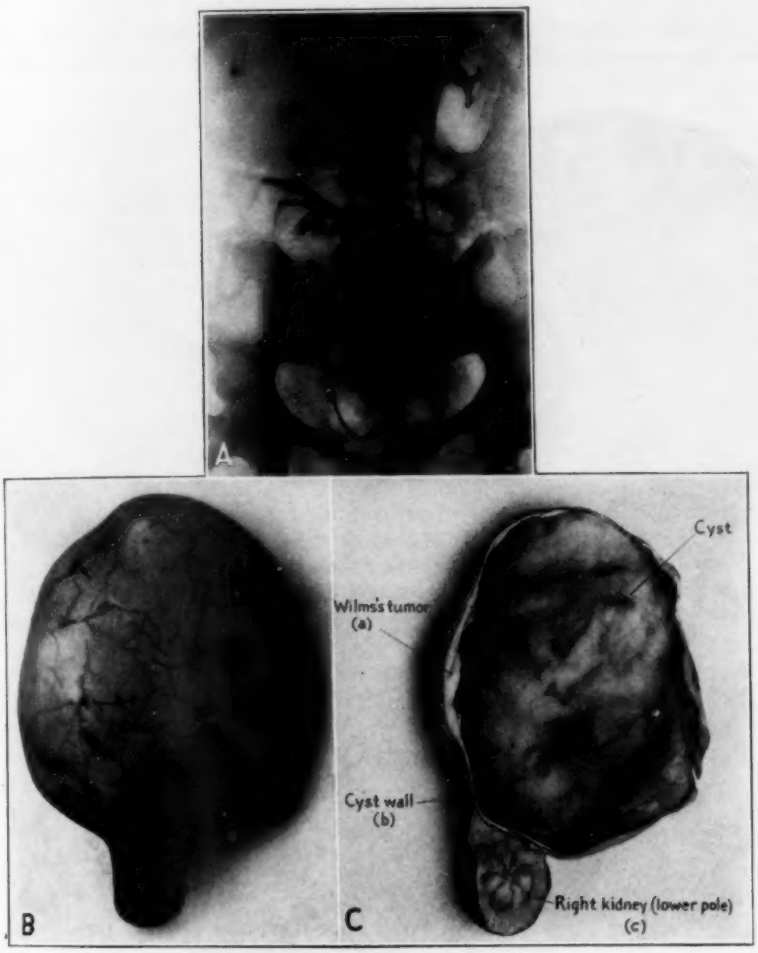

Fig. 6 (case 4).—A gigantic solitary renal cyst in a girl 18 years of age contained 5 liters of fluid and also within its walls Wilms's tumor. The cystic condition was diagnosed urographically and was confirmed at operation. *A*, bilateral pyeloureterograms revealing a normal kidney on the left side and congenital ectopy on the right with definite flattening of the upper calix, slight inward rotation of the renal plevis and displacement of the right ureter, strongly suggesting the presence of a large solitary cyst of the upper pole of the right kidney. *B*, drawing of the specimen removed at operation by transperitoneal nephrectomy, representing the enormous solitary cyst of the upper pole of the right kidney which completely destroyed the upper half of the organ. *C*, interior view of the gigantic cystic sac showing the smooth surface of the capsule of the cyst attached to the upper pole of the right kidney and revealing the association of a malignant growth with the benign cyst.

justified by the advanced destruction of the renal parenchyma, as the only means of obtaining permanent cure.

CASE 4.—*A gigantic solitary renal cyst with Wilms's tumor in a young girl was diagnosed urographically. Transperitoneal nephrectomy was performed, and*

Fig. 7 (case 4).—Photomicrographs of the histologic sections of the cyst and the kidney revealing: *A*, the typical structure of Wilms's tumor arising from the walls of the capsule of the cyst; *B*, Wilms's tumor and cyst wall; *C*, renal tissue, hyalinized capsule and tumor.

at the time of operation the specimen proved to be a large solitary cyst containing 5 liters of chocolate brown fluid. Attached to the base of the walls of the cyst was a malignant growth.

Miss M. S., 18 years old, was examined by Dr. E. J. Daly of Jersey City, N. J., who gave me permission to report the case. The patient's chief com-

plaint was moderate pain on the right side of the abdomen, not radiating to the right lower quadrant, associated with nausea of three weeks' duration. On physical examination there was a large cystic mass which was not tender and which filled the entire abdomen. The left kidney was not palpable. The patient underwent exploratory laparotomy on Feb. 6, 1936, when appendectomy was performed, with removal in addition of a small ovarian cyst. On April 4, 1937, she was readmitted after having suffered a fall flat on the abdomen, after which the persistent pain became more severe and was again accompanied by nausea and vomiting. The clinical and the laboratory findings were noncontributory. Roentgenograms of the chest and the gallbladder and a series of gastrointestinal roentgenograms, including some in making which enemas of barium sulfate were used to obtain visualization, also failed to reveal any abnormalities except deviation of the transverse colon, which looked as if it was pushed downward by an abdominal tumor mass. At this time the patient received a complete urologic and urographic examination. Intravenous urograms disclosed that the pelvis of the right kidney was displaced downward and was low in position. Cystoscopy and retrograde pyelography revealed a congenital ectopic kidney on the right side situated almost at the level of the sacrum and the crest of the ilium; the pelvis was rotated downward and inward. A lateral pyelogram also disclosed flattening of the upper calix; this suggested a filling defect produced by compression of the cyst or the tumor attached to the right kidney (fig. 6*A*). Another exploratory laparotomy was performed, during the course of which transperitoneal nephrectomy was carried out successfully; the right kidney was removed with an enormous cyst the size of the head of a fetus attached to its upper pole (fig. 6*B*). The specimen removed at operation contained 5 liters of chocolate brown fluid. Examination of the cystic fluid revealed the presence of many red blood cells and occasional white blood cells. There was no evidence of urea; this proves that while the cyst arose from the renal parenchyma, it in no way communicated with the upper calices or the renal pelvis. When the cystic cavity was opened, a flat infiltrating tumor was found attached to the wall of that part of the cyst which was adherent to the renal parenchyma (fig. 6*C*). Histologic examination revealed that this was Wilms's tumor (fig. 7).

This case illustrates the association of a malignant growth with a large solitary cyst of the kidney; such a possible association must always be kept in mind in treating younger persons. Nephrectomy in these cases is the procedure of choice for removal of the malignant tumor.

CASE 5.—*A bilocular left renal cyst was diagnosed urographically.*

Mrs. H. A. R., a housewife aged 66, consulted me on Sept. 18, 1939, about her complaints of shortness of breath, high blood pressure, severe pain in the precordial region and difficult respiration. She had been receiving treatments for obesity and for the cardiac and aortic condition for several years. She complained also of frequency of urination day and night, chronic constipation and slight pain and dulness in the left side of the abdomen radiating to the left lumbar region. On physical examination the right kidney was slightly palpable; the left kidney was low in position and easily palpated. Apparently, the left kidney was larger and lower down than the right. Urinalysis disclosed the presence of an alkaline reaction, traces of albumin, few hyaline casts and leukocytes with clumps; an occasional red blood cell and many bacteria also were present.

In view of these urologic findings a complete urographic examination was recommended. Roentgenograms and intravenous urograms, taken at Doctors Hospital on Oct. 4, 1939, revealed that the right kidney was normal in size, shape and position. The left kidney was lower in position than the right. In a fifteen minute film the pelvis appeared to be bifid in type. There was an overshadow in the outer border suggesting the presence of a large solitary cyst about the size of an orange. There was another round shadow which seemed to push the ureter inward, indicating the presence of another cyst in the lower pole of the same kidney. Although the diagnosis was evident from the intravenous urograms, retrograde pyelograms were recommended to confirm it. However, as the patient's general symptoms had improved with medical care, she left town without further examination.

From the urographic point of view, the diagnosis was definitely that of bilocular large solitary cyst of the kidney. Since, however, the diagnosis was not confirmed by retrograde pyelograms or proved at operation, this case is reported only to illustrate the possibility of urographic diagnosis.

CASE 6.—*A solitary cyst of the lower pole of the left kidney was diagnosed urographically.*

S. F., a man 41 years of age, consulted me on May 10, 1933, about indefinite pain in his abdomen. He also complained of frequency of urination day and night, dysuria, nervousness, dyspepsia and chronic constipation. Twenty years previously he had an attack of similar pain, for which appendectomy had been done. He stated that he had nevertheless been suffering from these symptoms off and on during all that period. The urine was clear, but microscopically it contained a few pus cells and red blood cells. The prostate was found to be normal by rectal palpation. The right kidney was not palpable; the lower pole of the left kidney was barely made out. The external genitals were normal. Roentgenograms and intravenous urograms revealed an anomaly of the twelfth rib on the left side, in that this rib was much shorter than the corresponding rib on the right side. Intravenous urograms revealed the presence of a small cyst about the size of a tangerine at the level of the lower pole of the left kidney which was deviating the course of the ureter inward. There was also slight compression of the lower calix, which appeared crescent shaped. The urographic diagnosis was that of large solitary cyst of the lower pole of the left kidney.

Retrograde pyelography was recommended but was not carried out. The diagnosis of large solitary cyst was therefore not confirmed or proved at operation. The patient's symptoms subsided under proper medical care, and he left town without a complete urologic check-up.

CASE 7.—*A large solitary cyst of the upper pole of the left kidney was diagnosed urographically and treated by puncture and aspiration of the fluid.*

J. O., a young man 19 years of age, consulted Dr. J. W. Draper, who permits me to report this case, on Jan. 29, 1938. The patient's chief complaint was urethral discharge. The past history was irrelevant except that he had at times had difficulty in voiding. On physical examination hypospadias with the meatal opening about 1 cm. back from the tip of the glans penis was noted. A smear taken from the hypospadiac meatus was positive for gonococci. The discharge responded to local instillation and sulfanilamide therapy. However, there remained some

shreds in the urine and pus cells in the prostatic secretion. At the end of four months the patient was taken to New York Hospital for a complete check-up. During the course of this examination intravenous urograms disclosed a crescent-shaped defect in the pelvis and the upper calices of the left kidney; this suggested the presence of a renal cyst of moderate size (fig. 8 *A* and *B*). At that time needle aspiration was done and 120 cc. of clear straw-colored fluid removed from the renal cyst. The examination of the fluid for urea yielded negative results. Aspiration of the cyst was not continued because the patient fainted during the procedure. It was not until a year later that another roentgenogram was taken and the cyst again aspirated. Urograms showed the same crescent-shaped filling defect compressing the upper calices and the renal pelvis; they gave the impression of a large serous cyst of the kidney about the size of a grapefruit. At this time the cyst was punctured, and 750 cc. of clear fluid was aspirated. After this

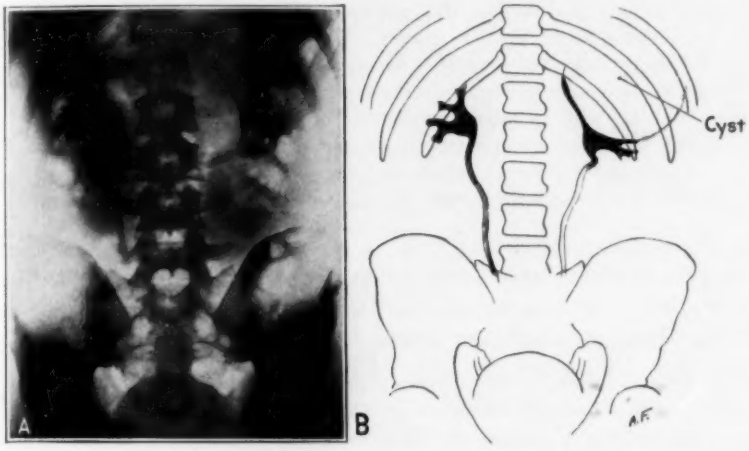

Fig. 8 (case 7).—A large serous cyst of the upper pole of left kidney in a boy 19 years of age was diagnosed by intravenous urography and confirmed by puncture and aspiration of the cyst. *A*, intravenous urogram disclosing a normally functioning kidney on the right and a crescent-shaped compression and elongation of the upper calix on the left side, suggesting the diagnosis of a large solitary renal cyst; this was confirmed by aspiration of 750 cc of fluid, although no operative confirmation was available. *B*, drawing to indicate the anatomic position and the topographic relations of the cyst.

last aspiration the patient left town, and nothing is known regarding his present condition.

Intravenous urograms led to a diagnosis of large solitary cyst of the kidney. Needle aspiration of the fluid confirmed the diagnosis, since it was obvious that the fluid had been drawn from a large serous cyst of the kidney, although no operation was carried out in this case.

CASE 8.—*A large solitary cyst of the lower pole of the left kidney was diagnosed urographically.*

G. M. M., a man 62 years of age, consulted me on Jan. 3, 1934, about his complaint of left renal colic. He gave a history of having had hematuria and renal

colic twenty years previously, when he passed a small urinary calculus and of having had the same condition again three years before consulting me. During the last twenty years he suffered with a mild pain, which at times became severe, in the area of the left kidney region. On physical examination the abdomen was distended. The right kidney was not palpable. The left kidney was enlarged, readily palpated and tender on pressure. A soft round mass about the size of a large grapefruit could be definitely made out on palpation and apparently was attached to the lower pole of the left kidney. The prostate was enlarged and boggy in consistency. Urinalysis revealed the presence of microscopic pyuria, a few red blood cells, albumin, bacteria and hyaline casts. There was no shadow indicative of stone anywhere in the urinary tract except a certain amount of calcification surrounding the large shadow in the area of the left kidney; this appeared to be a calcification in the capsule of a cyst in that organ. Intravenous urograms disclosed destruction of the left renal pelvis and the lower calices where a crescent-shaped shadow gave the impression that a large solitary cyst was attached to the lower pole of the left kidney. There was also considerable deviation of the left ureter toward the midline, which was in contact with the vertebral column. The patient left town after the diagnosis of cyst of the left kidney. He returned on Nov. 6, 1937, when another intravenous urogram was taken. This examination disclosed the same large round cystic mass causing a filling defect of the left renal pelvis and the lower calices and thus sustained the diagnosis of large solitary cyst of the left kidney made on previous examination.

Urographic studies as well as clinical observation clearly disclosed the presence of a large solitary cyst in the lower pole of the left kidney. Since, however, the patient had no further symptoms relating to the kidney ailment, he did not return for further treatment.

CASE 9.—*A large solitary cyst in the lower pole of the right kidney with a double renal pelvis was diagnosed by retrograde pyelograms.*

Mrs. C. R., a housewife 55 years of age, was referred to me for examination on Nov. 18, 1935, complaining of pain in the right lumbar region of two months' duration with frequency of urination day and night. She gave a history of having had pyuria, pyelitis and cystitis in 1930 and again in 1932. For several intermittent attacks of pain she had roentgen examination of the gallbladder and the gastrointestinal tract elsewhere. Urinalysis showed evidence of microscopic pyuria and hematuria and a trace of albumin. On physical examination the right kidney was low in position, readily palpable and tender on pressure. The left kidney was not palpable. On Nov. 20, 1935, she was examined cystoscopically; at that time a diagnosis of stricture of the urethral meatus and polyposis of the bladder neck was made. Retrograde pyelograms disclosed right nephroptosis with a renal pelvis of the bifid type and some compression of the lower calices by a rounded superimposed shadow about the size of an orange which suggested the presence of a large solitary cyst in the lower pole of the right kidney. A pyelogram showed the left kidney was normal.

This patient was treated medically and urologically for the condition of the urethral meatus and bladder neck, but since she refused the suggested kidney operation and left town, the diagnosis of large solitary cyst of the right kidney could not be confirmed surgically.

CASE 10.—*A large solitary cyst in the lower pole of the right kidney was diagnosed by pyeloureterograms.*

Mr. E. F., 74 years of age, was referred to me for examination on March 10, 1937, complaining of pain in the right lumbar region of two weeks' duration. The pain radiated to the front and down along the line of the ureter. He had frequency of urination day and night. The voided specimen of urine was clear with a few shreds. Urinalysis disclosed the presence of pus cells and red blood cells as well as traces of albumin. On physical examination the abdomen was distended. The right kidney was low in position, easily palpable and tender on pressure; the left kidney was not palpable. The prostate gland was found by rectal examination to be slightly enlarged and leathery in consistency. There was about 1 ounce (29.5 cc.) of residual urine. The urethra was permeable to sound F. 22. On March 17, 1937, the patient was examined cystoscopically, both ureters were catheterized, and roentgenograms were taken with catheters and instrument in position. Both kidneys had good eliminatory function with regard to urea estimation and phthalein elimination. Pyelography disclosed a crescent-shaped defect, with flattening of the pelvis and downward rotation, and absence of the calices and a round shadow covering the lower pole of the right kidney. The right ureter was also displaced slightly inward, and the position of the kidney was lower than that of the left kidney, which was normal. The pyelocalicial defect produced by compression and the good-sized circumference suggested the presence of a large solitary cyst of the right kidney. A pyelogram of the left kidney showed that it was bifid in type but otherwise normal.

While the pyelographic diagnosis of large solitary cyst of the lower pole of the right kidney was definitely made, it was not confirmed by operation, since the patient was relieved by medical care and since in view of his advanced age and lack of urinary symptoms no operation was advised.

TREATMENT

In regard to the treatment of large serous cyst of the kidney, three different methods must be considered: (1) medical treatment followed by close urologic and urographic observation; (2) treatment by aspiration or injection, which is always to be condemned as fallacious; (3) surgical treatment, which may be either conservative or radical.

Medical Treatment.—In the medical treatment, there must be considered those uncomplicated cases in which the cyst has been an accidental roentgen finding, is asymptomatic, is still of rather small size, has not displaced the organ or caused any compression of the calices, the renal pelvis or the ureter and has not interfered with the function and the normal drainage of these organs; those cases in which there is no evidence of associated disease in the kidney and in which urinalysis or microscopic examination of the catheterized specimen reveals no pus, blood or micro-organisms; those cases in which urographic examination shows that there is no connection of the cyst with the excretory apparatus of the kidney, and finally, those cases in which repeated pyelographic studies show conditions that are within normal limits.

In early cases the asymptomatic cyst may not require any open or surgical treatment but only proper clinical observation from time to time in order that the physician may be assured that the cystic sac is not undergoing a silent rapid growth or causing any further pathologic change. As a rule, urographic studies repeated from time to time will serve to disclose accurately enough the progress of a harmless lesion, and if there is any doubt, the kidney and cyst should be exposed by operation for proper treatment.

Treatment by Aspiration or Injection.—In the so-called nonsurgical treatment of large serous cyst of the kidney, many authors of pre-urographic days advocated puncture with aspiration and injection of the cyst as a panacea. However, this method of treatment, as commonly carried out in the past, has often resulted in serious complications and even death, as one can see from the literature. Thus Lejars reported 4 deaths among 7 patients treated by the method of needle aspiration and injection. Of the 3 patients who survived, none was completely cured of his ailment. In 1906, Simon reported his own use of puncture in the treatment of 5 patients; 4 died, and only 1 survived. Thompson also reported a death following the repeated tapping of an enormous solitary cyst of the kidney.

These considerations led Albarran, Péan, Tuffier and other surgeons of that epoch to give up this unsound and uncertain method of treatment. This so-called harmless procedure should in no way be compared with the simple method of injection and aspiration treatment of hydrocele of the tunica vaginalis, since the kidney is anatomically a deep thoraco-abdominal organ in which the long needle cannot safely be allowed to penetrate in the dark of a closed surgical wound, where it may produce complications and even death through profuse bleeding, formation of renal hematoma and development of peritonitis. The physician may have the sad experience that the sac refills again and that the procedure must be repeated with great inconvenience and discomfort to the patient. It is evident today that this form of treatment is only palliative and not in any sense curative; further, the aspirated fluid can in no way reveal associated disease that may be present, such as a possible malignant growth. Although the method may have its diagnostic possibilities, it should not be considered a routine mode of treatment except in unusual circumstances.

Surgical Treatment.—In the surgical treatment of large solitary serous cyst of the kidney consideration must be given to the type of lesion that may be present in the cyst and the kidney and also to the functional capacity of the organ. Two essential groups of cases are found: (1) those in which a conservative operation can be performed

to save the kidney and (2) those in which a radical operation is indicated for the removal of the kidney and the cyst.

So much progress has been achieved in modern surgical urology since the introduction of pyelography that it is now possible to make an accurate preoperative diagnosis of large solitary cyst of the kidney in most instances. It is therefore obvious that with this type of benign and localized lesion of the kidney the ideal procedure is a conservative operation designed to save as much of the renal parenchyma as possible by simple total removal of the renal cyst.

Conservative Operations: In the group of cases in which conservative treatment is possible, three main types of operation are indicated (fig. 9).

1. When the solitary serous cyst is located in the upper pole, is rather small and not connected with the upper calix, as in case 1 of the series here reported, the kidney and the cyst are surgically exposed by the usual incision in the lumbar region; this is followed by complete nephrolysis and ureterolysis. The cyst is then clamped and aspirated under full vision and resected by scissors from its line of attachment to the upper pole of the kidney. The capsule of the kidney in contact with the surface of the base of the cyst (which has already been removed) is sutured around the kidney by interrupted sutures, and nephropexy is carried out, the upper pole of the kidney being fixed to the eleventh intercostal space in order that the kidney may be brought high up into its normal anatomic position (fig. 9*I*). It is worthy of note that in case 1 retrograde pyelograms taken one year after this conservative operation disclosed that the renal pelvis and the calices had entirely recovered their normal form and that the kidney had regained its normal position and function.

2. The second type of conservative operation is particularly suitable for use in those cases in which the benign large solitary serous cyst is situated in the external border of the middle portion of the renal parenchyma; also for use in an occasional case in which the cyst is connected with or so closely attached to one of the calices of the renal pelvis that at the time of operation the calix has to be clamped and tied by transfixed sutures to prevent leakage of urine. The technic of the operation consists in partial renal decapsulation, incising the kidney capsule all around the cyst, finding the line of cleavage and then enucleating the cyst from its renal bed; after this the base of the kidney is clamped and sutured to prevent bleeding or leakage of urine (fig. 9*II*). Once the cyst has been removed, the two halves of the renal parenchyma are approximated by interrupted sutures, and a transplanted piece of fat or muscle is placed in the center of the wound to prevent hemorrhage or leakage.

3. When the large solitary serous cyst is found in the lower pole of the kidney and has by its compression destroyed a considerable amount of renal parenchyma, and there is no line of demarcation, it is necessary

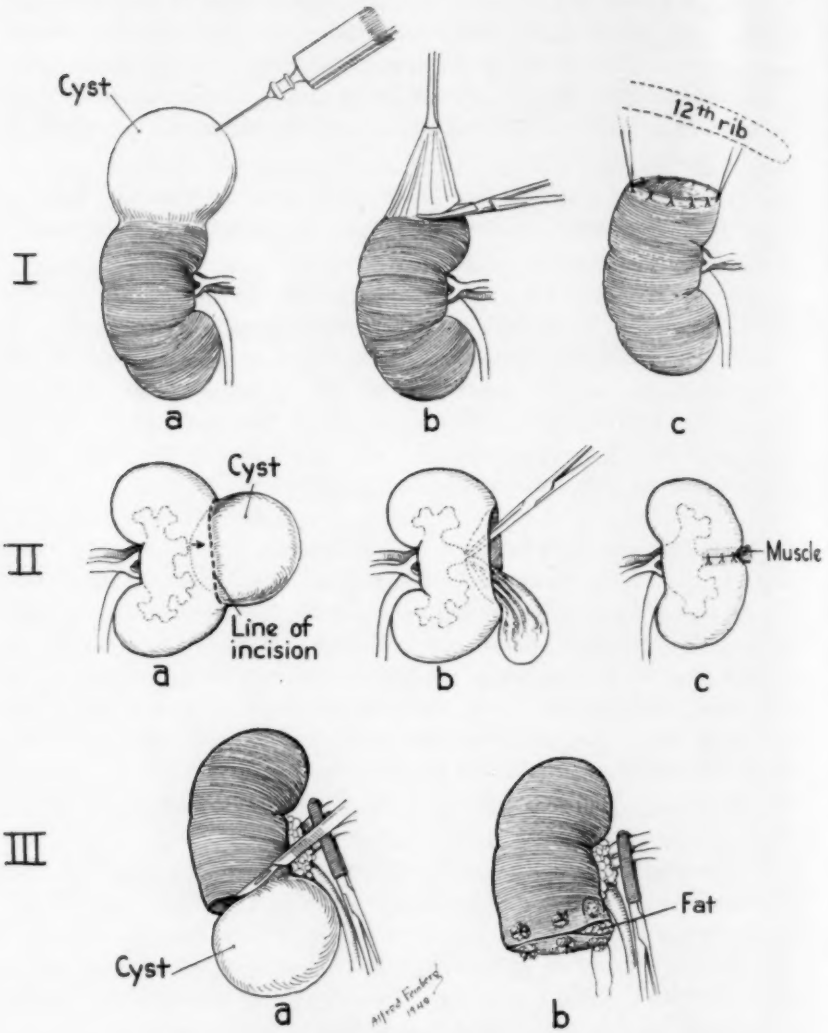

Figure 9

(See legend on opposite page)

to carry out polar amputation, cuneiform resection, heminephrectomy or partial nephrectomy for the removal of the cyst (fig. 9*III*). In this type of operation, it is essential to clamp the pedicle with a rubber-shod clamp to prevent hemorrhage from the kidney before performing partial

nephrectomy for removal of the closely adherent cyst. The cut surface of the kidney is then covered with a piece of fat to prevent bleeding, and mattress sutures are placed.

4. Marsupialization of the cyst was recommended by a number of authors in the preurographic era, when the differential diagnosis and the type of cyst could not be established preoperatively. Although this conservative surgical procedure of marsupializing as much of the cyst as possible has its indications in difficult cases, e. g., when the cyst cannot be surgically exposed at the time of operation, and is also useful when combined with nephrostomy in complicated cases in which there is evidence of infection with hydronephrosis or pyonephrosis, it has the

TABLE 2.—*Analysis and Results of Surgical and Nonsurgical Treatment in Ten Cases of Large Solitary Cyst of the Kidney* *

Type of Treatment	Patients Cured	Patients Improved	Patients Not Followed Up	Total Number of Patients
Resection of cyst from upper pole of right kidney with nephropexy	1	..	..	1
Lumbar nephrectomy	2	..	..	2
Transperitoneal nephrectomy	1	..	..	1
Puncture with aspiration of cyst	..	1	..	1
Cystoscopic treatment with dilation of ureters and lavage of kidney pelvis	..	2	..	2
Medical treatment	..	..	3	3
Total	4	3	3	10

* Summary: Of 4 patients operated on, all are cured; of 6 patients not operated on, 3 were improved and 3 not followed up.

EXPLANATION OF FIGURE 9

Operative technic for excision of a large solitary cyst of the kidney:

I. The kidney and the cyst of the upper pole are exposed by a lumbar incision. (*a*) The cyst is aspirated under vision. (*b*) The cyst is clamped and resected. (*c*) Interrupted sutures are placed all around the kidney between the base of the cyst and the fibrous capsule of the kidney; this is followed by nephropexy for suspension of the organ. This procedure was successfully carried out in case 1 (see text).

II. The cyst is located on the external borler of the kidney and is close to a calix. (*a*) The fibrous capsule of the kidney is incised all around the cyst; this is followed by partial decapsulation to gain the line of cleavage of the cyst in its renal bed. (*b*) The cyst has been emptied as in *I;* its base close to a calix is clamped, and the calix is sutured to prevent leakage of urine or bleeding. (*c*) The cyst having been removed, a piece of muscle is interposed between the cut surfaces, and the kidney is sutured as in ordinary nephrotomy.

III. The large cyst at the lower pole has destroyed a considerable amount of parenchyma by compression. (*a*) The pedicle of the kidney is clamped with a rubber-shod clamp, and partial nephrectomy is accomplished to remove the closely adherent cyst. (*b*) The raw surface of the kidney is covered with fat to prevent bleeding, and mattress sutures are placed (see text).

disadvantage, nevertheless, of being followed by a lumbar fistula of long standing, which usually requires secondary nephrectomy to obtain permanent cure. Hence it seems best whenever possible to perform one of the three conservative operations already described.

Radical Operations: In the radical surgical treatment of large solitary serous cyst of the kidney, two types of nephrectomy are indicated: the usual extraperitoneal lumbar nephrectomy and the transperitoneal nephrectomy. The latter is more suitable for voluminous cysts that resemble renal neoplasms, as in 1 of the cases reported in this paper. Nephrectomy should be carried out (1) when the kidney is devoid of function, (2) when the cyst has destroyed more than one half or one third of the organ by compression, (3) when there is a short renal pedicle or there are insufficient blood vessels to supply the remaining portion of the organ, (4) when there are obvious technical obstacles to the performance of a conservative operation and (5) when there is evidence of concomitant lesions in the kidney suggestive of a renal neoplasm. Under any of these conditions nephrectomy should be performed, provided that the kidney of the opposite side is functionally and pyelographically normal.

SUMMARY AND CONCLUSIONS

Large solitary cyst of the kidney was formerly regarded as rare, but since the adoption of the systematic use of urography it is known to be of not infrequent occurrence. The condition can now be diagnosed preoperatively in most instances and should be differentiated from other types of cyst and from associated borderline lesions of the kidney. A clinicoanatomopathologic classification of cystic conditions that may be found in the kidney or in the region of the kidney is presented in table 1. This table serves to emphasize the different types of large solitary cyst of the kidney according to number, size and anatomic location, and especially according to type of lesion and nature of content. It also serves to differentiate three main groups, demonstrable urographically and anatomopathologically, according as the cyst is connected or is not connected with a calix or the renal pelvis or lies in fact altogether outside the kidney structure but within the anatomotopographic region.

The pathogenesis of the large solitary cyst is uncertain, although it is clear that the condition may be either congenital or acquired.

This study with the report of 10 cases has revealed that the symptoms are various and insidious. The condition may be diagnosed urographically, even for patients who have no urinary symptoms or only mild ones, whenever the cyst by compression has produced marked painful symptoms or physical signs of a tumor mass palpable in one or the other

side of the abdomen. Such a condition plainly demands urologic and urographic examination.

The most common roentgenographic and urographic observations in making the diagnosis of large solitary cyst of the kidney are as follows: (1) compression of the renal pelvis or of one or more calices; (2) change in the position of the axis of the kidney; (3) inward displacement of the ureter; (4) displacement or rotation of the renal pelvis, upward or downward; (5) visualization of the shadow of the cyst; (6) crescent shape of the kidney pelvis or of a calix; (7) calcification of the cyst walls in some cases; (8) visibility of the psoas muscle through the walls of the cyst; (9) shadow of the cyst superimposed on the kidney shadow; (10) visualization of the cyst furnished by pyelovenous backflow.

While this benign localized lesion has in the past been considered harmless, experience shows that from time to time cases are encountered in which a malignant tumor is concealed within the walls of the cyst. This fact justifies the insistence on open surgical exploration to verify the diagnosis and on removal of the cyst by conservative operation when possible or radical procedure when necessary, not only to prevent further symptoms but also to remove any possibility of extension of a malignant growth. With a tumor of the kidney, the pyelogram as a rule shows more marked invasion of the calices and the renal pelvis, since the growth of the tumor extends inward to occupy the renal parenchyma, while the cyst tends to spread outward. A pyelogram of a tumor of the kidney presents a more disorganized and more bizarre appearance, following no such rule of uniformity as that of a large simple cyst. Furthermore, in the case of such a cyst the shadow of the kidney itself is usually not enlarged, whereas the shadow of the kidney is considerably increased if there is a malignant tumor of that organ.

In this series of 10 cases, 4 patients were operated on, with curative results. In 1 case the operation was resection of the cyst from the upper pole followed by right nephropexy. In 2 cases extraperitoneal lumbar nephrectomy was done and in 1 a transperitoneal nephrectomy, all with gratifying results. Of the 6 patients not operated on, 3 were improved, and 3 were not followed up.

The youngest patient was a woman 18 years of age and the oldest a man 74. There were 5 women and 5 men. The diagnosis in 4 cases was made by intravenous urography and in 4 others by retrograde pyelograms. In the 2 remaining cases urography failed to reveal the cyst, and the diagnosis was made during operation for nephropexy.

The cyst was located in the upper pole of the right kidney in 2 cases, in the upper pole of the left kidney in 2, in the lower pole of the right kidney in 3 and in the lower pole of the left kidney in 3.

It was striking to note that in the 2 cases in which the diagnosis was not made before operation the patients were women in whom the right kidneys were low in position and readily palpable on physical examination and the urographic studies revealed marked pyelectasis, caliectasis and evidence of pyelonephritis and right nephroptosis. In 1 of these 2 cases, the cyst was in the upper pole of the right kidney, and in the other, in the lower pole. In the first of these (case 1) resection of the upper pole of the right kidney followed by nephropexy relieved all symptoms and resulted in the permanent cure of a patient who had had two abdominal operations ten and twelve years previously for the same symptoms, both times without relief. In the other case (case 3), owing to anomalies of the blood supply, nephrectomy was necessary and resulted in cure.

In case 2 of this series a diagnosis of left renal neoplasm had been made elsewhere for the patient, who had marked hypertension and an attack of painless hematuria. However, according to my urographic findings the preoperative diagnosis was large sercus cyst of the upper pole of the left kidney, and this was confirmed at operation.

Case 4 is a vivid illustration of the possibility of a large solitary cyst of the kidney enclosing a malignant growth within its walls. The patient was a girl 18 years of age, who had undergone exploratory laparotomy elsewhere; at that time the appendix and a small ovarian cyst had been removed. About a year later, after injury from a fall, acute abdominal symptoms developed. She was then hospitalized and submitted to urographic examination which disclosed a gigantic cyst at the upper pole of the right kidney. The cyst was removed by transperitoneal nephrectomy. Examination of the specimen disclosed Wilms's tumor within the cyst.

In case 7 the diagnosis of large solitary renal cyst was made by intravenous urography and confirmed by puncture and aspiration of the fluid. On the first puncture 120 cc. of clear fluid was aspirated, and on the second puncture, one year later, 750 cc. The aspirated fluid, which was of clear amber color, contained no urea, but the actual lesion underlying the cyst remained unknown for lack of surgical approach.

In the remaining 5 cases the diagnosis was definitely made urographically and substantiated by clinical observation, although in none of these cases was operation performed.

Finally, it appears that when there are enough urologic symptoms and when the preoperative urographic diagnosis has been made, the ideal course is to advise open surgical exploration of the kidney and the cyst by laparotomy with a view to resection of the cyst by one of the conservative operations described, in order to save the kidney and eliminate all possible complications or further disease that may jeopardize

the life of the organ. Even in borderline cases this appears to be the safest course. Then, in cases in which the kidney cannot be saved by conservative surgical procedures, nephrectomy will still remain as a last resort.

Drs. F. B. Lopez of Habana, Cuba, E. J. Daly of Jersey City, N. J., and J. W. Draper of New York Hospital permitted the report of cases 3, 4 and 7, respectively. Dr. H. R. Muller of Doctors Hospital made the histologic sections in case 2, of which photomicrographs are presented.

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EFFECT OF ASPHYXIA CAUSED BY BOWEL DISTENTION ON THE CONCENTRATION OF THE BLOOD

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Fine [1] and associates showed that bowel distention maintained for many hours causes marked concentration of the blood. They asserted that this cannot be explained by dehydration or by intraperitoneal loss of fluid. In their most recent publication they stated that they have been unable to account for it.[2] (We have repeated many of their experiments with results the same as they reported.) In our other paper [3] on this general subject we presented experimental and clinical findings which showed that the intraperitoneal loss of blood protein is considerable when the bowel is inflated by pressures which we believe act on the human bowel in cases of acute obstruction. We observed some local loss when we used the pressures which Fine employed. However, this loss is not sufficient in most cases to account for the great concentration of the blood which occurs after prolonged inflation of the intestine. Further, this concentration occurs even when the pressure used is too low to damage the bowel. We planned the experiments hereinafter described to discover what causes this concentration of the blood.

PROTOCOLS OF EXPERIMENTS

SERIES 1 (6 dogs).—*Experiments to Show the General Effects of Prolonged Distention of the Bowel.*—Sodium amytal (50 mg. per kilogram of body weight) was given intravenously to produce light anesthesia. Laparotomy was done, and ligatures were applied to the pylorus and the ileocecal valve over the tubes which had been introduced into the intestine at these points. The bowel was inflated in various experiments with pressures ranging from 22 to 96 mm. of mercury. One pressure was used in each experiment. The pressure was maintained until the

1. Gendel, S., and Fine, J.: The Effect of Acute Intestinal Obstruction on the Blood and Plasma Volume, Ann. Surg. **110**:25-36, 1939.

2. Gendel, S., and Fine, J.: Plasma Transfusion in Intestinal Obstruction, Ann. Surg. **112**:240-248, 1940.

3. Gatch, W. D., and Battersby, J. S.: The Two Stages of Bowel Distention: A Study of Bowel Injury by Distention and Its Effect on Volume and Concentration of Blood, Arch. Surg. **44**:108-118 (Jan.) 1942.

dog died or showed unmistakable signs of the effects of the pressure. Blood pressures of some of these dogs were taken.

Results.—The blood pressure did not fall to a significant extent until shortly before death. Marked cyanosis of the mucous membranes developed in all the animals. The respiratory rate always increased, and the breathing became shallower as time passed. The higher pressures caused death much sooner than the lower.

Autopsy.—The quantity of fluid present in the peritoneal cavity was considerable in those dogs in which the higher pressures had been used. In these dogs gross signs of injury to the bowel were present in the form of subperitoneal hemorrhages, matting together of loops of bowel and albuminous exudate. The spleen was always hard and contracted. The bladder usually contained 100 to 150 cc. of urine. The heart, the lungs, the kidneys, the muscles and the subcutaneous tissues were normal. The most striking findings were general cyanosis and a tarry consistency of the blood.

Series 2 (4 dogs).—*Experiments to Determine Whether Nervous Impulses[4] Caused by Distention of the Bowel or Toxic Substances Absorbed from the Damaged Bowel Are Responsible for the Concentration of the Blood.*—The same procedures were employed as in series 1 except that all the blood vessels of the small intestine were divided between ligatures. In two experiments the entire small bowel was removed, and strips of Penrose tubing, 1 inch (2.5 cm.) in diameter and equal in combined length to the excised intestine, were then placed within the abdomen and inflated with a pressure equal to that used in the experiments on the intestine.

Results.—The results of these experiments were the same as those obtained in series 1.

Series 3 (3 dogs).—*Experiments to Determine Whether Inflation of the Stomach Has the Same Effect as Inflation of the Bowel.*—The same procedures were used as in series 1 except that ligatures were applied to the cardiac and the pyloric ends of the stomach, which was then inflated. In two experiments the stomach was inflated with a maintained pressure of 22 mm. of mercury. This caused the death of both dogs within three hours. At autopsy the stomach was observed to fill the entire abdomen in both dogs. In neither dog, however, did it show any gross sign of injury other than this marked distention, and in both it contracted considerably on deflation.

In a third experiment the stomach of a dog was inflated with a maintained pressure of only 15 mm. of mercury. This dog was killed at the end of six hours, when it was in a moribund condition. Its stomach was not so markedly distended as those of the other 2 dogs.

Results.—In general the results were the same as those in series 1 except that the animals died much sooner, there was no free fluid in the abdomen and the blood concentration was not so great. We found no fluid in the stomach or the peritoneal cavity of any of these dogs. Blood determinations obtained in this series are given in table 1.

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4. Fine, J.; Rosenfeld, L., and Gendel, S.: The Role of the Nervous System in Acute Intestinal Obstruction, Ann. Surg. **110**:411-416, 1939.

Conclusions.—The results of the experiments described show: (1) that distention of the bowel and distention of the stomach cause the death of the experimental animal under anesthesia induced by sodium amytal in a period of time which varies inversely with the amount of pressure used to distend the intestine or the stomach; (2) that concentration of the blood occurs; (3) that this concentration when low pressure is used can only in part be accounted for by the loss of fluid in the peritoneal cavity or by way of the kidneys, the bowel or the lungs.

The only explanation of this loss which we can conceive is that it is caused by the escape of blood proteins from capillaries in all parts of the body. This implies that distention of the bowel in some way injures the capillary endothelium of the body and permits the blood proteins to escape.

TABLE 1.—*Blood Determinations of the Dogs Submitted to Gastric Distention*

Dog	Weight, Kg.	Pressure Used in Gastric Distention, Mm. of Mercury	Oxygen Content of the Venous Blood, Volumes per Cent		Hematocrit Determinations per Cent		Duration, Hr.
			Normal	Final	Normal	Final	
1	8.6	22	17.3	3.9	46	50	3 (death)
2	14.1	22	16.7	12.3	42	49	3 (death)
3	13.6	15	11.5	8.1	53	70	6

Analysis of the blood after prolonged distention of the bowel shows that it has lost much more albumin than globulin. This indicates that the damage to the capillary endothelium is not so grave as that caused by burns or inflammation, since after these injuries the large globulin molecules escape as easily as the smaller albumin molecules. Further, it is well established that the experimental animal can recover from the effects of distention of the bowel if this has not been too prolonged. The results of the foregoing experiments make it inconceivable that distention of the bowel causes capillary damage by any neural mechanism or by the action of any toxic material produced in the distended bowel. These considerations led us to make the hypothesis that the damage to the capillaries is due to slowly developing asphyxia caused by distention of the bowel or stomach.

SERIES 4.—*Experiments to Determine the Effect of Distention of the Bowel on the Oxygen Content of Arterial and Venous Blood, as Well as the Effect on the Circulation Time.*—In this series hematocrit and venous and arterial blood oxygen determinations were made after distention of the bowel. The effect of distention

on the blood circulation time was ascertained by the sodium cyanide method; 0.5 mg. of sodium cyanide per kilogram of body weight was used.

Results.—The results of two experiments in this series are given in figure 1.

It is generally agreed that anoxia damages the endothelium.[5] How does distention of the bowel cause anoxia? Can anoxia alone cause blood concentration, and will the findings at autopsy be identical with those caused by distention of the bowel? The experiments in series 5, 6 and 7 were performed to answer these questions.

SERIES 5 (4 dogs).—*Experiments to Determine Whether Artificial Respiration or the Respiration of Pure Oxygen Can Prevent the Blood Concentration Caused*

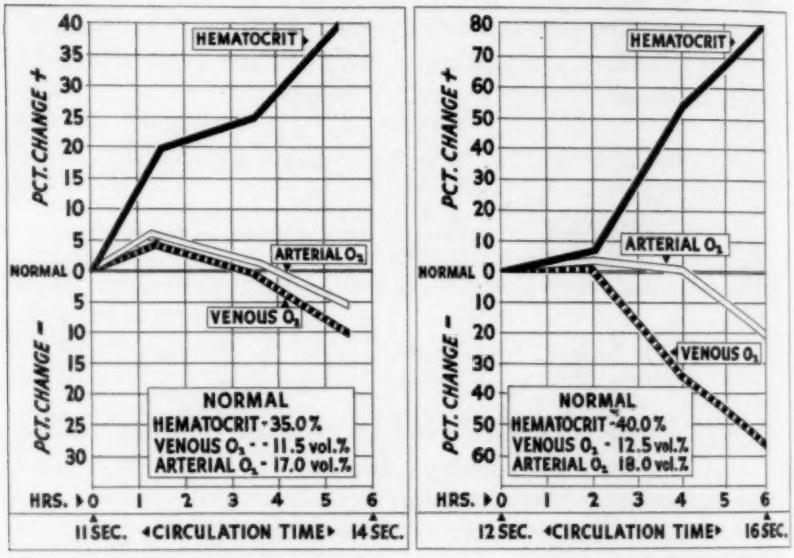

Fig. 1.—The effect of distention of the bowel on the oxygen content and circulation time of the blood.

by Distention of the Bowel.—The procedures were the same as in series 1 except that tracheotomy was done to facilitate artificial respiration and to administer pure oxygen. Artificial respiration was carried out on 2 dogs at the rate of 20 respirations a minute, and the quantity of air used to inflate the lungs of each dog was equal to the tidal air of the animal at the beginning of the experiment. A mercury manometer was connected with the apparatus to make sure that the lung was never inflated with a pressure greater than 6 mm. of mercury. The

5. Landis, E. M.: Micro Injection Studies of Capillary Permeability: III. The Effect of Lack of Oxygen on the Permeability of the Capillary Wall to Fluid and to Plasma Protein, Am. J. Physiol. **83**:528-542, 1928.

dogs given pure oxygen were not submitted to artificial respiration. The intraintestinal pressure used in all cases was 29 mm. of mercury.

Results.—The results are shown in table 2.

Conclusions.—Our conclusions from this series of experiments are: (1) that both artificial respiration and the administration of pure oxygen prolong the life of animals with distention of the bowel; (2) that both oppose but do not prevent blood concentration in animals with distention of the bowel; (3) that both mitigate but do not prevent asphyxia.

TABLE 2.—*Effects of Artificial Respiration and the Inhalation of Pure Oxygen on the Blood Concentration Caused by Distention of the Bowel*

Dog	Weight, Kg.	Pressure of Inflation, Mm. of Mercury	Oxygen Content of the Venous Blood, Volumes per Cent		Hematocrit Determination, per Cent		Duration, Hr.	Oxygen Capacity of the Venous Blood, Volumes per Cent	
			Normal	Final	Normal	Final		Normal	Final
			A. Artificial Respiration *						
1	15.7	29	10.5	7.8	49	57	7		
2	15.0	29	10.0	7.5	39	69	16	14.5	20.5
			B. Inhalation of Pure Oxygen						
3	16.3	29	15.6	10.9	45	58	5	20.0	27.2
4	14.1	29	16.4	12.6	38	54	6	18.3	22.3

* Artificial respiration was administered at the rate of 20 respirations per minute; the volume of tidal air was normal.

TABLE 3.—*Effect of Asphyxia Caused by Limiting the Volume of Tidal Air on the Blood Picture*

Dog	Weight, Kg.	Respirations per Minute	Tidal Air	Hematocrit Determination, per Cent		Duration, Hr.	Oxygen Content of the Venous Blood, Volumes per Cent	
				Initial	Final		Initial	Final
1	14.0	40	..	47	60	6	15.7	9.9
2	14.1	..	½	42	39	3 (death)	16.7	12.3
3	8.6	50	..	52	61	7	18.0	12.5

SERIES 6 (3 dogs).—*Experiments to Determine Whether a Moderate Degree of Asphyxia Produced by Limiting the Air Supplied to the Lungs Causes the Same Blood Picture and Presents the Same Changes at Autopsy as Distention of the Bowel.*—Sodium amytal (50 mg. per kilogram of body weight) was used to induce anesthesia. Tracheotomy was performed. Determination of the tidal air was made. Limitation was imposed on the tidal air, but in no case was this decreased by more than one half of its normal volume.

Results.—The results are given in table 3.

Conclusion.—Moderate and prolonged asphyxia caused by limiting the volume of the tidal air will produce the same blood picture and will present identical changes at autopsy as distention of the bowel.

SERIES 7 (6 dogs).—*Experiments to Determine the Systemic Effect of Distention Limited to Separate Parts of the Gastrointestinal Tract.*—Sodium amytal was used to induce anesthesia. Fluoroscopic examination was made of the thorax to determine the effects of (1) inflation of the stomach, (2) inflation of the entire small bowel and (3) inflation of the large bowel. The pressure used in all experiments was 29 mm. of mercury. We observed that inflation of the stomach caused marked elevation of the diaphragm, that inflation of the small bowel caused lesser elevation and that inflation of the large bowel caused no elevation.

We observed also that after inflation of the stomach or the small bowel there was a marked decrease in the movement of the ribs and a great increase in the rate of respiration.

In two experiments we measured the volume of the tidal air and recorded the rate of respiration while the small bowel was kept inflated with a pressure of 29 mm. of mercury.

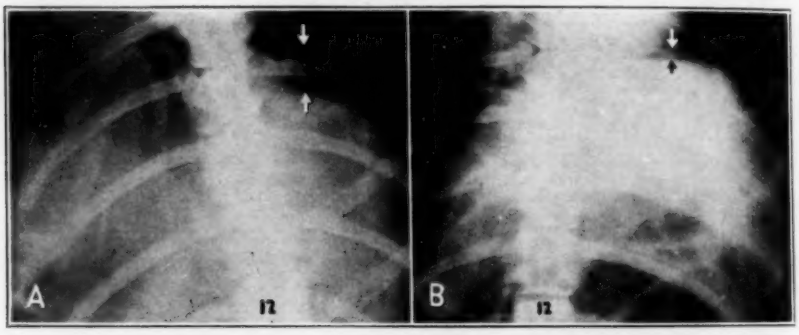

Fig. 2.—The effect of distention on the elevation and excursion of the diaphragm. *A*, normal; *B*, intestinal distention with elevation and limitation in the range of excursion.

TABLE 4.—*Effects of Distention Limited to the Small Bowel on the Respiration of a Dog*

Time of Determination	Respirations per Minute	Volume of Tidal Air, Cc.	Volume of Air Breathed per Minute, Cc.
Start	12	83	996
3 hours	26	90	2,340
6 hours	34	50	1,700

Results.—Results of one of the experiments are shown in table 4.

Despite the increased volume of air which these animals breathed, the oxygen in their blood steadily decreased, for their mucous membranes became more and more cyanotic. The truth of this observa-

tion is confirmed by the measurements made under similar conditions of the oxygen content of the venous and arterial blood of the animals in series 4.

We have shown (series 5) that neither artificial respiration nor the administration of pure oxygen can cause efficient oxygenation of the blood of animals with distention of the bowel. The demonstration of this effect of distention is sufficient for our present purpose; we plan a special study of its causes.

COMMENT

We conclude that asphyxia is the primary cause of death after prolonged distention of the stomach or small intestine. Concentration of the blood while distention is present is due to damage to the capillary endothelium of all parts of the body caused by the lack of oxygen.

It seems clear that asphyxia causes hemoconcentration and that hemoconcentration increases asphyxia. In two experiments in which the entire small bowel was inflated for eight hours we were able to prevent hemoconcentration by giving intravenously 100 cc. of plasma per hour. Both animals were in good condition at the end of this period. The experiments were ended because the supply of plasma was used up. Hemoconcentration is an important but secondary cause of death from distention. Asphyxia due to distention can cause death in the absence of serious hemoconcentration. We proved this at least for distention of the stomach.

Effects of distention similar to these in experimental animals must occur in human beings, but we are not as yet prepared to state how important they are in clinical practice.[6] Everyday experience in the laboratory shows that the dog is more quickly injured by interference with respiration than man.[7] The dire results of distention of the stomach are well known, and it seems probable to us that the mechanism we have studied is responsible for them.

While we have been engaged in this experimental work, we have observed several patients suffering from prolonged distention of the small bowel. In none of them did we observe concentration of the blood though none of them had been given blood or plasma. All, however, had continuous gastric lavage.

We recall seeing many patients who were suffering from severe embarrassment of respiration because of acute and rapidly developing

6. Fine, J.; Hurwitz, A., and Mark, J.: Clinical Study of Plasma Volume in Acute Intestinal Obstruction, Ann. Surg. **112**:546-556, 1940.

7. Gatch, W. D.; Mann, F. C., and Gann, D.: The Danger and Prevention of Severe Cardiac Strain During Anaesthesia, J. A. M. A. **60**:1273-1278 (April 26) 1913.

distention. This work should at least make us look for hemoconcentration in all patients with obstruction of the bowel and, if we find it, give plasma in adequate quantities.

CONCLUSIONS

Prolonged distention of the stomach and the small bowel with pressures too low to damage them results in death of the experimental animal. Asphyxia due to interference with respiration is the cause of death.

All the effects of distention can be produced by prolonged limitation of the air supply.

The blood concentration observed in these experiments is a result of, and aggravates, asphyxia, but is not the primary cause of death, which may occur without much concentration of the blood. Death is delayed when blood concentration is prevented by the administration of adequate quantities of plasma.

Distention of the stomach is more rapidly fatal than distention of the small bowel; distention of the large bowel is comparatively harmless. These effects depend on the degree of interference with respiration caused by distention of these parts of the gastrointestinal tract.

The full clinical importance of these experimental observations has not been determined.

MATERIALS FOR INTERNAL FIXATION OF INTRACAPSULAR FRACTURE OF THE NECK OF THE FEMUR

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The advantages of internal fixation of fractures of the intracapsular neck of the femur as compared with less satisfactory methods of immobilization formerly widely used are acknowledged by most orthopedic surgeons and by those general or traumatic surgeons who are sufficiently trained in the discipline of aseptic surgery and the principles of the healing of fractures to be able to apply with skill and judgment one of the many widely described technics. The confusion today is concerned primarily with the fact that each of many surgeons has designed, used and recommended his own variation of wire, pin, screw or gadget for maintaining position after reduction of a fracture of the femoral neck.

Much of the widespread interest in internal fixation of fractures of the hip must be credited to Smith-Petersen,[1] who described, used successfully and popularized the three-flanged nail.

The average incidence of union from all methods of internal fixation, including small nails,[2] small threaded pins or wires,[3] larger smooth pins,[4]

From the Department of Surgery, University of Chicago.

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Read before the Section on Orthopedic Surgery at the Ninety-Second Annual Session of the American Medical Association, Cleveland, June 5, 1941.

1. Smith-Petersen, M. N.; Cave, E. F., and Vangorder, G. W.: Intracapsular Fractures of the Neck of the Femur, Arch. Surg. **23**:715-759 (Nov.) 1931.

2. Moore, A. T.: Fracture of the Hip Joint (Intracapsular): A New Method of Skeletal Fixation, J. South Carolina M. A. **30**:199-205 (Oct.) 1934; Fractures of the Neck of the Femur, South. Surgeon **8**:139-147 (April) 1939; Fracture of the Hip Joint, Surg., Gynec. & Obst. **64**:420-436 (Feb., no. 2 A) 1937.

3. Compere, E. L., and Lee, J.: The Restoration of Physiological and Anatomical Function in Old Ununited Intracapsular Fractures of the Neck of the Femur, J. Bone & Joint Surg. **22**:261-277 (April) 1940. Compere, E. L.: The

(Footnotes continued on next page)

two-flanged [5] or three-flanged nails,[6] small screws,[7] large screws,[8] the lag screw [9] and other pins or spikes,[10] has been greater than 80 per cent. After experience with several different types of the materials most commonly used, including the Smith-Petersen nail, it became obvious to us that there were both disadvantages, in part theoretic and in part practical, and certain advantages to be obtained from each.

Theoretically, the ideal method for the internal fixation of intracapsular fracture of the neck of the femur should meet the following requirements: (1) Immobilization should be sufficiently well maintained to prevent refracture, angulation at the site of fracture or displacement with separation of fracture fragments. (2) The internal fixation should be sufficient in itself so that neither plaster cast nor long immobilization in bed following reduction and fixation will be necessary. (3) Intact nutrient arteries in the neck or the head of the femur should not be endangered by the forceful insertion of chisels or even of a nail or a screw which is greater in diameter than is really essential for maintaining immobilization. (4) The pin, screw or nail selected should not needlessly displace cancellous bone and should not grossly obstruct attempts at revascularization. (5) Materials used for immobilization should obtain a sufficient degree of fixation so that they will neither migrate

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Ambulatory Treatment of Recent Fractures of the Intracapsular Neck of the Femur Following Threaded Wire Fixation, J. Internat. Coll. Surgeons **3**:401-410 (Oct.) 1940. Telson, D. R., and Ransohoff, N. S.: Treatment of Fractured Neck of the Femur by Axial Fixation with Steel Wires, J. Bone & Joint Surg. **17**:727-738 (July) 1935.

4. Sofield, H. A.: Fracture of the Neck of the Femur Treated by the Steel Pin Method of Fixation, Illinois M. J. **71**:200-204 (March) 1937.

5. Cubbins, W. R.; Callahan, J. J., and Scuderi, C. S.: Fractures of Neck of Femur; Open Operation and Pathologic Observations; New Incision and New Director for Use of Simplified Flange, Surg., Gynec. & Obst. **68**:87-94 (Jan.) 1939.

6. Campbell, W. C.: Internal Fixation in Fractures of the Neck of the Femur, Ann. Surg. **105**:939-952 (June) 1937. Smith-Petersen, Cave and Vangorder.[1]

7. Thomas, T. T.: Fixation by a Wood Screw Without Arthrotomy in Certain Fractures of the Neck of the Femur, Am. J. Surg. **35**:292-295 (Sept.) 1921.

8. Lippmann, R. K.: Corkscrew-Bolt for Compression-Fixation of Femoral Neck Fractures, Am. J. Surg. **37**:79-87 (July) 1937.

9. Henderson, M. S.: Internal Fixation for Recent Fractures of Neck of Femur, S. Clin. North America **19**:927-942 (Aug.) 1939.

10. Gaenslen, F. J.: Subcutaneous Spike Fixation of Fresh Fractures of Neck of Femur, J. Bone & Joint Surg. **17**:739-747 (July) 1935; Fracture of the Neck of the Femur, J. A. M. A. **107**:105-114 (July 11) 1936. Wescott, H. H.: A Method for the Internal Fixation of Transcervical Fractures of the Femur, Virginia M. Monthly **59**:197-204 (July) 1932; Method for Internal Fixation of Transcervical Fractures of Femur, J. Bone & Joint Surg. **16**:372-378 (April) 1934. Knowles, F. L.: Fractures of the Neck of the Femur, Wisconsin M. J. **35**:106-109 (Feb.) 1936.

forward into the acetabulum and the pelvis (as has happened in too many cases in which small smooth pins or wires have been used) nor become loosened and displaced outward as the patient becomes active and ambulatory on crutches, because immobilization would thus be lost and nonunion result.

One of us (Compere [8]) has reported aseptic necrosis of the head of the femur following the insertion of a Smith-Petersen nail, although union of the fracture was obtained. This has also been demonstrated by Campbell,[6] and the role played by the nail through possible injury to nutrient blood vessels or through prevention of revascularization during the months in which the three blades of the nail remained in situ has been postulated.

Our early experience in the use of Kirschner wires was most unsatisfactory because when the patients were permitted to become ambulatory on crutches, several or all of the wires became dislodged and migrated outward. This has also been the experience of others.[11]

The purpose of this study has not been to compare by test all of the many varieties of pins, nails, screws or gadgets. Reports of the successful use of small, threaded, drill point, stainless steel wires and the theoretic reasons for our choice of this method of internal fixation of fractures of the intracapsular neck of the femur have been included in earlier papers.[8]

The question which we have tried to answer has been merely this: Is it possible to obtain uniformly satisfactory immobilization of an intracapsular fracture of the neck of the femur through the use of three highly tempered stainless steel wires, gage .080, with fifty-six threads to the inch (2.5 cm.)?

We undertook to study the breakdown force of hips obtained at necropsy, fractured and pinned with three of the threaded wires. Later, the distraction force, or the pull in pounds required to separate completely the fracture fragments after pinning, was also studied. It then seemed advisable to learn whether the three threaded wires compared favorably in efficiency with the more widely used flanged nails or the stronger but nonthreaded round pins or nails. We selected the Smith-Petersen three-flanged nail and the nonthreaded round Steinman pins for comparison because of their known tensile strength.

PROCEDURE

Arrangements were made to obtain the entire proximal end of each femur of patients subjected to necropsy at the Cook County Infirmary. The postmortem examinations were performed from three to seventeen days after death; the average time was eight days. Some of the patients from whom these specimens were obtained had been bedridden or in a wheel chair for several months to as long

11. Selig, S.: Objections to the Use of Kirschner Wire for Fixation of Femoral-Neck Fractures, J. Bone & Joint Surg. **21**:182-186 (Jan.) 1939.

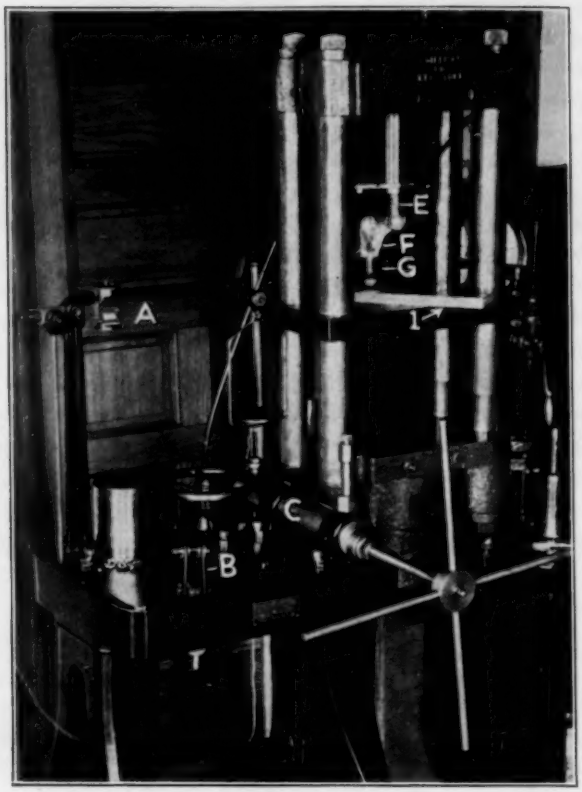

Fig. 1.—Machine used for testing fracture and breakdown forces: *A*, scale (weight balance); *B*, revolving motor-driven piston; *C*, hand-worked pressure cylinder; *E*, plaster cap over femoral head to prevent point pressure; *F*, a fresh femoral head, neck and trochanters; *G*, the shaft of the femur embedded in plaster in a metal cup; *I*, oak plank.

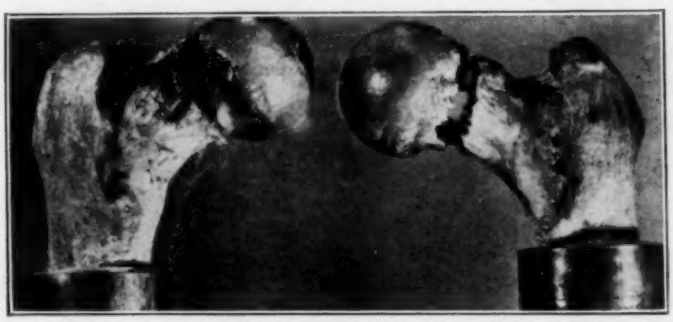

Fig. 2.—Photograph of two hips obtained at necropsy, mounted in plaster cups and then fractured by direct pressure force.

as nine years prior to death. Most of them had been elderly. The bone in the region of the neck of the femur was therefore atrophied from disuse, even to a greater extent than that which is usually found in a patient who has been sufficiently active to be ambulatory at the time of sustaining a clinical fracture. The hips were freed of all soft tissue attachments with a minimal amount of trauma to the periosteum. Neither dissolving, decalcifying nor fixating chemicals were used. Each hip was mounted in a round metal cylinder, approximately 5 cm. in diameter, and fresh plaster of paris was poured around the shaft. A second, concave mold

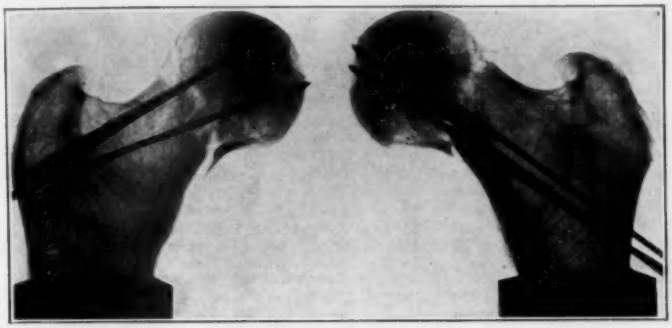

Fig. 3.—Roentgenogram of the hips of a 51 year old laborer who was ambulatory until one week before death, showing the position of the three threaded wires after pinning of the fracture fragments.

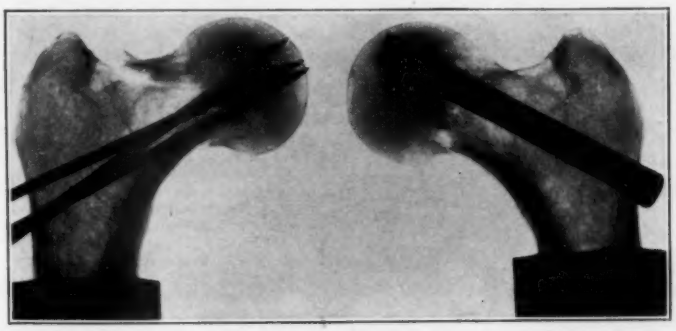

Fig. 4.—Roentgenogram of the hips of a 54 year old laborer who had been bedridden for several months before fracture, taken after reduction and pinning of the left hip with three Steinman pins and of the right hip with a Smith-Petersen nail.

was applied over the head of the femur so that force could be directed against the femoral head over a wide surface and local infraction be avoided.

Study of the fracture force and subsequently of the breakdown force after pinning was made possible through the aid of Dr. J. J. Prochaska and the Illinois Institute of Technology. The machine used for creating the fracture force was a hydraulic press designed for testing the tensile strength of wood and metals (fig. 1). The concave plaster cap was brought down with increasing force on the head of the femur until a fracture occurred (fig. 2). In some instances the fracture was subcapital, but in most of the experiments the fracture line was

oblique from the superior edge of the head downward and laterally toward the lesser trochanter. The number of pounds of pressure required to produce the fracture was recorded in each instance; this we have described as the fracture force. The fractured hips were repinned in as nearly anatomic position as possible (fig. 3).

TABLE 1.—*Data on Cases in Which Three Threaded Wires Were Introduced into Each Hip After Fracture*

Case	Hip	Fracture Force		Breakdown Force		Comment
		Lb.	Kg.	Lb.	Kg.	
1	Right	1,408	638.7	690	313	The patient was a 69 yr. old laborer; weight, 120 lb. (54.4 Kg.); ambulatory to day of death; acute hemorrhage into myocardium
	Left	1,640	743.9	1,488	674.9	
2	Right	680	308.4	480	217.7	The patient was an 89 yr. old housewife; weight 90 lb. (40.8 Kg.); bedridden six months; multilocular empyema
	Left	904	410	510	231.3	
3	Right	2,340	1,061.4	768	348.4	The patient was a 78 yr. old laborer; weight, 160 lb. (72.6 Kg.); ambulatory until four days before death; coronary thrombosis
	Left	2,208	1,001.5	558	258.1	
4	Right	2,400	1,088.6	252	114.3	The patient was a 51 yr. old laborer; weight 140 lb. (63.5 Kg.); ambulatory until a week before death; syphilitic aortic aneurysm and bronchopneumonia
	Left	2,460	1,115.8	432	196	
5	Right	564	255.8	186	84.4	The patient was a 67 yr. old laborer; weight, 130 lb. (59 Kg.);bedridden two months; old midthigh amputation on right side; right femur atrophied from disuse; arteriosclerotic cardiovascular disease; hypostatic pneumonia
	Left	1,674	759.3	372	168.7	
6	Right	1,728	783.8	420	190.5	The patient was a 53 yr. old laborer; weight, 135 lb. (61.2 Kg.); bedridden one month; cancer of the rectum with metastasis
	Left	1,638	742	360	163.2	
7	Left	2,220	1,007	330	149.6	The patient was a 44 yr. old man, a cook; weight, 120 lb. (54.4 Kg.); ambulatory until two days before death; massive bilateral fibroid tuberculosis
8	Left	1,140	517	300	136	The patient was a 64 yr. old printer; weight, 75 lb. (34 Kg.); in bed three months before death; anatomic diagnosis: pernicious anemia, healed pulmonary tuberculosis, multiple diverticula of small bowel
9	Left	1,440	653	320	145.1	The patient was a 42 yr. old man; weight, 100 lb. (45.4 Kg.) in wheel chair many months before death; unilateral pulmonary tuberculosis
10	Left	2,019	915.4	330	149.6	The patient was a 61 yr. old laborer; weight, 165 lb. (74.8 Kg.); bedridden period unknown; arteriosclerotic cardiac disease and generalized arteriosclerosis
11	Right	2,100	952.5	330	149.6	The patient was a 46 yr. old switchman; weight, 130 lb. (59 Kg.); bedridden seven months cirrhosis of the liver and mucous colitis
12	Left	1,260	571.5	270	122.5	The patient was a 49 yr. old laborer; weight, 112 lb. (50.8 Kg.); ambulatory until death; anatomic diagnosis: bilateral pulmonary fibroid tuberculosis and bilateral tuberculous pleuritis
13	Left	1,620	734.8	240	108.8	The patient was a 72 yr. old man; weight, 100 lb. (45.4 Kg.); ambulatory until two months before death; hypertensive cardiac disease and generalized arteriosclerosis
Average		1,655	750.7	455	206.4	

Nineteen hips were pinned with threaded wires, 5 with Steinman pins and 4 with a Smith-Petersen nail (fig. 4).

RESULTS

The results of these tests are shown in tables 1, 2 and 3. The threaded wires compared favorably with the larger nail or pins in resisting the breakdown force.

The wires were inserted transversely in one hip and obliquely from below upward in the other hip from each of 6 consecutive necropsies. We were surprised to find that the wires placed transversely resisted the

TABLE 2.—*Data on Cases in Which Three Steinman Pins Were Introduced into Each Hip After Fracture*

Case	Hip	Fracture Force		Breakdown Force		Comment
		Lb.	Kg.	Lb.	Kg.	
1	Left	1,344	609.6	152	68.9	The patient was a 54 yr. old laborer; weight, 120 lb. (54.4 Kg.); bedridden several months; pelvic neoplasm and bronchopneumonia
2	Right	2,760	1,251.9	480	217.7	The patient was a 61 yr. old laborer; weight, 165 lb. (74.8 Kg.); bedridden period unknown; arteriosclerotic cardiac disease and generalized arteriosclerosis
3	Left	1,800	816.5	270	122.5	The patient was a 46 yr. old switchman; weight, 130 lb. (59 Kg.); bedridden seven months; cirrhosis of the liver and mucous colitis
4	Right	1,320	598.7	360	163.2	The patient was a 49 yr. old laborer; weight, 112 lb. (50.8 Kg.); ambulatory until death; anatomic diagnosis: bilateral pulmonary fibroid tuberculosis and bilateral tuberculous pleuritis
5	Right	1,620	734.8	600	272.2	The patient was a 72 yr. old laborer; weight, 100 lb. (45.4 Kg.); ambulatory until two months before death; anatomic diagnosis: hypertensive cardiac disease and generalized arteriosclerosis
Average		1,769	802.4	372	168.7	

TABLE 3.—*Data on Cases in Which a Smith-Petersen Nail Was Introduced into Each Hip After Fracture*

Case	Hip	Fracture Force		Breakdown Force		Comment
		Lb.	Kg.	Lb.	Kg.	
1	Right	1,026	465.4	582	264	The patient was a 54 yr. old laborer; weight, 120 lb. (54.4 Kg.); bedridden several months; pelvic neoplasm and bronchopneumonia
2	Right	2,340	1,016	300	136	The patient was a 44 yr. old man; a cook; weight, 120 lb. (54.4 Kg.); ambulatory until two days before death; massive bilateral fibroid tuberculosis
3	Right	1,260	571.5	270	122.5	The patient was a 64 yr. old printer; weight, 75 lb. (34 Kg.); in bed three months before death; anatomic diagnosis: pernicious anemia, healed pulmonary tuberculosis, multiple diverticula of small bowel
4	Right	1,200	544.3	240	108.9	The patient was a 42 yr. old man; weight, 100 lb. (45.4 Kg.); in wheel chair many months before death; anatomic diagnosis: unilateral pulmonary tuberculosis
Average		1,456	660.4	348	157.8	

breakdown force much more effectively than those inserted obliquely. The average breakdown force of 6 hips pinned with wires in the transverse position was 723.6 pounds (328.2 Kg.). For the 6 contralateral hips pinned with obliquely placed wires the breakdown force was 452 pounds (205 Kg.), a difference of 271 pounds (123 Kg.).

In a smaller series of hips the holding power was tested. This was accomplished by calculating the force in pounds required for pulling the

head and the neck of the femur apart at the line of fracture after pinning with the Smith-Petersen nail, three threaded wires or three Steinman pins inserted in the usual crisscross or toe nail fashion (fig. 5). Although the wires were small and the threading fine, the holding power was greater than that of either the Smith-Petersen nail or the three large Steinman pins (table 4). This would tend to confirm our previous clinical observations that threaded wires which do not taper but maintain a uniform diameter throughout their length obtain a better grasp of the

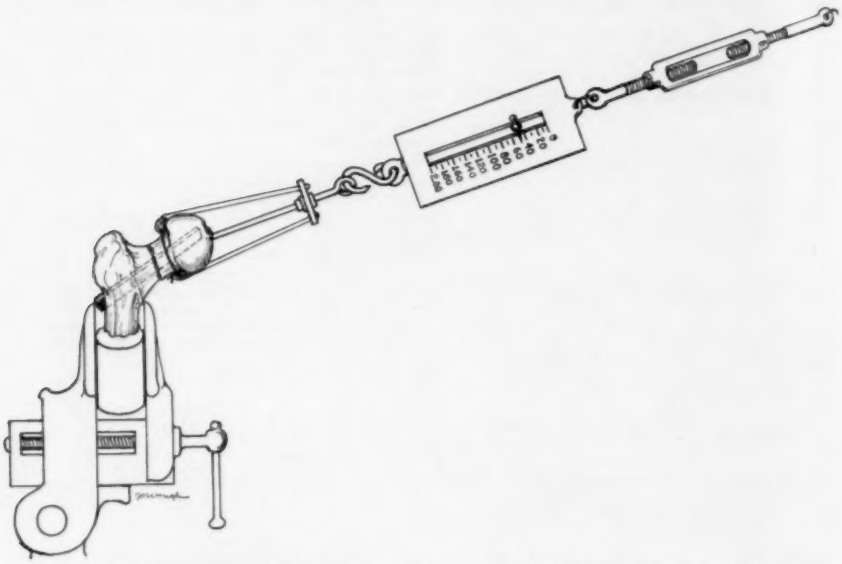

Fig. 5.—Diagrammatic illustration of the method of determining the distraction force required to separate the fracture fragments after pinning.

TABLE 4.—*Comparative Holding Power of Nails, Pins and Wires*

	Hip	Age of Patient, Yr.	Distraction Force *	
			Lb.	Kg.
Smith-Petersen nail				
Case 1	Left	72	70	31.8
Case 2	Right	72	60	27.2
Case 3	Right	54	20	9.1
Average			50	22.7
Three Steinman pins				
Case 1	Right	53	63	28.6
Case 2	Right	?	20	9.1
Case 3	Left	63	147	66.7
	?	?	120	54.4
Average			87	39.5
Three threaded wires				
Case 1	Right	49	140	63.5
Case 2	Right	64	112	50.8
Case 3	Left	53	170	77.1
Case 4	Right	46	95	43.1
Case 5	Left	72	80	36.3
Case 6	Right	63	100	45.4
Average			116	52.6

* Force required to pull fracture fragments apart after pinning.

bone and show less tendency to migrate than materials which are not threaded (fig. 6). A comparison of threaded wires, Steinman pins and the three-flanged nail as to breakdown resistance and holding power is shown in table 5.

We did not make these tests with Moore nails because they also are threaded where they engage the cortex of the femur, they are of small diameter, and they, too, may be inserted in toe nail fashion. The holding

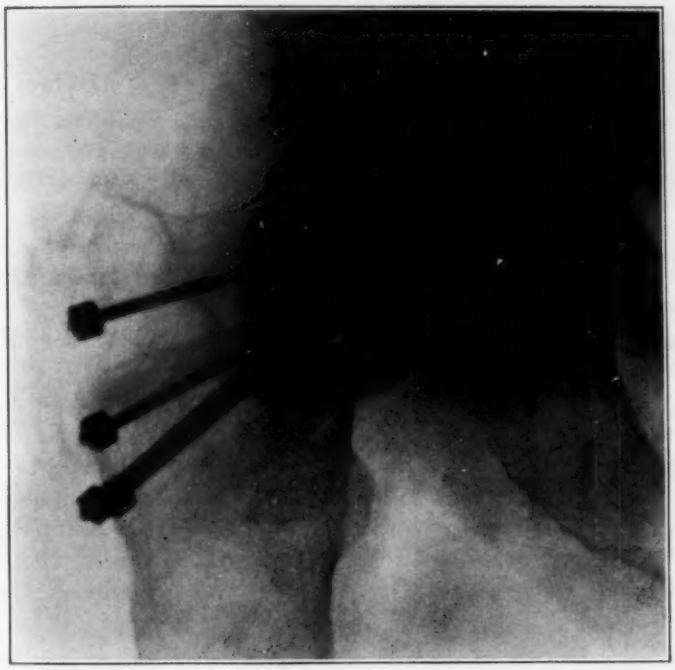

Fig. 6.—Roentgenogram of a hip of a patient aged 71 years after reduction and internal fixation with four threaded steel wires. In each of the breakdown or holding tests the wires remained firm in the femoral head but shredded through the bone of the trochanter and the shaft when the immobilization was disrupted by pressure or by distraction force. For that reason, a round stainless steel nut, illustrated in this roentgenogram, is now used on each wire and tightened firmly against the femoral cortex. When the wire is cut, the threads are flattened, thus holding the nut in place.

TABLE 5.—*A Comparison of the Smith-Petersen Nail, Steinman Pins and Threaded Wires*

	Average Fracture Force		Average Breakdown Force		Average Distraction Force	
	Lb.	Kg.	Lb.	Kg.	Lb.	Kg.
Smith-Petersen nail	1,456	660.4	348	157.8	50	22.7
Three Steinman pins	1,769	802.4	372	168.7	87	39.5
Threaded wires	1,655	750.7	455	206.4	116	52.6

power of Moore nails has been proved by clinical test, and we consider that they are mechanically and theoretically comparable to the threaded wires. We have preferred the wires because of the ease of insertion with a Stille-Scanlon-Kirschner drill. We also suggest that the holding power of the threads on the portion of the wire that enters the head fragment may be of some value in maintaining secure immobilization.

COMMENT

Von Langenbeck [12] was the first to suggest internal fixation of a recent fracture of the neck of the femur, and Koenig [13] succeeded in nailing such a fracture and reported his results in 1878. In 1889, Senn [14] reported success in the use of a large iron carpenter's nail and taught the principle and advantages of immediate reduction and permanent fixation of a fracture of the neck of the femur by this method. A few years later, Nicolaysen [15] reported with a remarkable degree of modesty a series of 13 successful cases in which he spiked a fractured femoral neck with a three-cornered nail driven directly through the skin but added to this procedure plaster cast immobilization.

The modern surgeon has a wide choice of materials from which to select one for his own uses in pinning fractured hips. The surgeon should first of all be well grounded in the physiology of bone. His responsibility and interest should extend beyond mere healing of the fracture. He should seek to bring about this result with the least possible trauma to the structures with which he is dealing. He should have concern for blood supply to the neck and the head of the femur and guard against doing anything which might increase the hazard of late aseptic necrosis. Devitalization of the head of the femur will nullify an otherwise excellent surgical result, even after union of the fracture has been obtained. A surgeon should think of results in terms of the patient's ability to use the limb with strength, movement and freedom from pain in the years that are to follow treatment.

SUMMARY AND CONCLUSIONS

Three small threaded stainless steel wires accurately placed afford strong immobilization for intracapsular fractures of the neck of the femur. The holding power of three small threaded steel wires is greater than that of the Smith-Petersen nail or of larger, nonthreaded Steinman pins.

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12. von Langenbeck: Verhandl. d. deutsch. Gesellsch. f. Chir. **7** (pt. 1):92, 1878.

13. Koenig, in discussion on von Langenbeck.[12]

14. Senn, N.: Treatment of Fractures of the Neck of the Femur by Immediate Reduction and Permanent Fixation, J. A. M. A. **13**:150-159 (Aug. 3) 1889.

15. Nicolaysen, J.: The Diagnosis and Treatment of Fractures of the Neck of the Femur, Nord. med. ark. (no. 16) **8**:1-19, 1897.

The insertion of threaded steel wires produces minimal trauma to cancellous bone of the neck or the head of the femur. These wires are unlikely to injure nutrient blood vessels, and they constitute no real obstruction to revascularization. Wires inserted transversely immobilize more securely than those placed obliquely from below upward.

This method has been used successfully both in the treatment of recent fracture of the neck of the femur without any cast and with almost immediate ambulation and also in conjunction with tibial bone grafts in the treatment of old ununited fractures of the neck of the femur without its being necessary to apply a plaster cast or use other methods of external immobilization. Judged by clinical as well as experimental test, the use of threaded steel wire is as satisfactory a method for the internal fixation of fractures of the intracapsular neck of the femur as other methods which have been described or observed.

The small threaded wire technic will continue as our method of choice because it is mechanically efficient and because we believe it to be physiologic, relatively atraumatic and less likely to contribute to delayed aseptic necrosis than methods requiring grosser trauma and greater displacement of cancellous bone of the fracture fragments.

Small threaded nuts on each wire may be tightened securely against the lateral cortex of the femur. This has been observed to increase the efficiency of the immobilization.

ABSTRACT OF DISCUSSION

Dr. Harold R. Bohlman, Baltimore (presenting oral discussion for Dr. Austin T. Moore, Columbia, S. C.): Dr. Moore has treated 197 fractures of the hip, 70 per cent of which have been intracapsular, with no observation of nonunion since 1937.

He wishes to stress the following points: first, the necessity for perfect reduction; second, the need for impaction; third, the absolute necessity for rigid fixation, and fourth, drilling of the neck through the fracture site to reestablish circulation and facilitate healing.

He has enunciated the principle of four pins and feels that the fourth pin adds more than 25 per cent strength when the pins are properly placed. His principle of placing the pins parallel but spaced about the periphery of the neck is a point which he wishes to bring out emphatically. In this I agree with him from my experiments with the modulus of torsion in various types of internal fixation. The four pins when properly spaced about the periphery of the neck prevent eccentric movement and sheering stresses, which are great factors in producing nonunion of the neck of the femur by breaking down capillary bridging and thus starting the process of absorption of the neck.

Dr. Moore has checked the breaking forces and states that his figures are similar to those of Dr. Compere and associates.

The threaded wires of Dr. Compere give a great deal of fixation because there is a greater bearing surface and because when placed more transversely, they take care of the distraction force at the top of the neck or the area of tension. For this reason they may be placed more transversely than the rigid pins. The rigid pins have to depend on an oblique or an acute angle, because any further impaction

of the head or absorption in the line of fracture allows the proximal portion of the neck and the head to slide down on the pins.

Dr. Moore is thoroughly in accord with the feeling that pins and wires impact less bone than do flanged nails or larger appliances. Whatever the appliance, sheering stresses must be avoided. Wires and pins can be more easily removed and reinserted than flanged nails when readjustment is necessary.

Dr. Rudolph S. Reich, Cleveland: Since the advent of the flanged Smith-Petersen nail I have used it in cases of fracture of the hip in which internal fixation was indicated. This method has superseded for me the many pins, screws and nails which were previously recommended, and my results have been much more satisfactory.

I was particularly struck by the comments Dr. Compere made regarding the occurrence of aseptic necrosis after the use of the Smith-Petersen nail. Since there are no exact statistics, it cannot be postulated that this occurrence is due to the use of the three-flanged nail. It may be due to the fact that the percentage of good results is larger since the introduction of the Smith-Petersen nail. Nevertheless, the occurrence of aseptic necrosis has concerned me considerably. Whether it is due to real damage to the circulation of the neck or the head of the femur cannot be determined. In my experience there have been cases in which aseptic necrosis in intracapsular fractures of the hip healed without any internal fixation.

I have a question I wish Dr. Compere would answer for me: Is the force that he exerted on these necks of femurs analogous to the force that is exerted when the hip is fractured? I wonder whether the force he used is not more a torsional than a distracting force.

I have not used Dr. Compere's threaded nails so I cannot report the results of any such experience. I should be interested to know what the end results will be. If the incidence of aseptic necrosis is reduced, I shall be happy to be converted from the three-flanged Smith-Petersen nail to the threaded nail of Dr. Compere.

Dr. Edward L. Compere, Chicago: I am aware that the force which was exerted to produce these experimental fractures and repeated to test the breakdown strength or the holding power of the threaded wires or nails is not identical to that which clinically produces fractures of this type. I was primarily interested in testing the holding power of the wires, and believe that this was adequately demonstrated.

Although this method of internal fixation may decrease the incidence of aseptic necrosis, it will not prevent it entirely. The first patient treated by this technic has come into my office since this study was written. He complained of a little lameness in the hip. A roentgenogram revealed aseptic necrosis with the beginning of collapse of the head of the femur.

However, I do believe that it is justifiable to seek a method of internal fixation which is least likely to cause additional injury to the blood supply or to prevent revascularization.

I wish to emphasize that if a surgeon treats fracture of the hip, his responsibility and interest should extend beyond the mere healing of the fracture. He should be concerned about the blood supply to the head of the femur. He should not think of results in terms of immediate union of the fracture, but he should follow the patient for many years. Only in that way can he know exactly how effective any plan of treatment is. He should think of the end result in terms of the patient's ability to use the limb with strength, movement in the articulation and freedom from pain in the years to come.

ROLE OF ABDOMINAL DISTENTION IN LEUKOCYTE EXHAUSTION

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SYRACUSE N. Y.

In a previous article[1] I reported 7 cases of leukocytic exhaustion characterized by leukopenia with a normal differential count and an extreme neutrophilic shift to the left. In 3 cases (cases 1, 2 and 3), the white cell failure followed either overwhelming or prolonged infection, but in the other 4 (cases 4, 5, 6 and 7) there was no such strain on the marrow to account for the blood picture. It was assumed, therefore, that in the latter group some impairment in leukopoietic power had been present all along, and these patients were considered to have a low leukocyte reserve. In 2 of the cases in which there was supposed low leukocyte reserve (cases 6 and 7), marked abdominal distention was present at the time of the lowest counts, and it was thought even at that time that some relation existed between the abdominal findings and the blood picture, though no explanation was offered as to its nature.

Since then 4 additional cases have been observed in which leukocytic exhaustion as defined appeared in the absence of severe infection and in the presence of marked abdominal distention. In case 2, hereinafter to be described, this association occurred on two separate occasions.

REPORT OF CASES

CASE 1.—H. C., a white man aged 30 years, was admitted to the Hospital of the Good Shepherd, Syracuse University, on Sept. 23, 1937, with symptoms of acute appendicitis of eighteen hours' duration.

The past history was not significant except for an attack at the age of 10 years of what was considered appendicitis.

Physical examination bore out the diagnosis of appendicitis in a well developed normal-appearing adult. No abdominal distention was present.

Table 1 shows that there was moderate preoperative leukocytosis with the expected differential picture. Preoperative urinalysis showed nothing abnormal.

At operation, performed shortly after admission, the appendix was removed in spite of its normal appearance, since no definite cause for the preoperative symptoms could be found. The pathologic report read: "Result of examination of appendix, negative."

On the morning after the operation abdominal distention was present and began to increase steadily. By September 26, the third postoperative day, distention was so marked that it required intestinal intubation with continual suction.

1. Van Duyn, J., II: Leukocytic Exhaustion Following Surgical Procedures, Arch. Surg. **37**:302 (Aug.) 1938.

On September 27, a blood count was made which showed a low total white cell count with a marked neutrophilic shift to the left. On the following day injections of 6 cc. of concentrated extract of liver were started and continued for three days; in all, eight injections were given. The white cell count increased somewhat during this time, but the shift to the left continued extreme (table 1).

Throughout this period of marked distention, beginning on September 27, the urine showed increased concentration, persistent albumin (2 to 3 plus) and numerous casts of all types. The twenty-four hour output was reduced, ranging from 380 to 745 cc. during the four days beginning September 26.

The temperature rose gradually from an initial level of 100 F. to a range of 102 to 103 F. by September 30.

A roentgen plate of the abdomen taken on September 27 showed distention of the small intestine, cecum and ascending colon.

By September 30, seven days after the appendectomy, no improvement had taken place, and exploratory laparotomy was advised. At this operation the small

TABLE 1.—*Leukocyte Counts of the Patient in Case 1*

Date	White Blood Cell Count	Neutrophils, per Cent	Lymphocytes, per Cent	Monocytes, per Cent	Eosinophils, per Cent	Nonfilamented Neutrophils, per Cent	Comment
9/23	16,000	83	14	3	0	Under 25	Before first operation
9/26	.....	..	..	..	..	..	Marked distention
9/27	5,000	66	23	7	3	96	Basophils, 2 per cent
9/28 a.m.	5,400	55	39	6	0	96	
p.m.	5,300	67	23	5	5	95	Injections of extract of liver started
9/29 a.m.	7,700	70	18	12	0	97	
p.m.	10,000	70	19	10	1	96	
9/30 a.m.	10,500	55	30	13	2	92	Before second operation
p.m.	5,700	57	22	21	0	92	
10/1 a.m.	12,500	70	20	10	0	86	Blood transfusion
p.m.	14,200	70	25	5	0	77	

intestine was found markedly distended, and the colon, moderately so. There was no evidence of peritonitis. After operation the temperature rose sharply to 106.8 F. The course continued rapidly downhill, and the patient died on the following day. Necropsy was not performed.

CASE 2.—First Admission: C. L., a white woman aged 38 years, was admitted to the Hospital of the Good Shepherd, Syracuse University, on June 13, 1937, with a typical history of acute appendicitis of forty-eight hours' duration.

The past history revealed nothing unusual; the patient had always been healthy and active.

Physical examination confirmed the diagnosis of appendicitis but revealed nothing else significant.

The preoperative white blood cell count showed leukocytosis and an increase in the percentage of neutrophils as expected (table 2).

At operation, performed immediately, a gangrenous but unruptured appendix was removed, and the peritoneal cavity was drained. The pathologic report read: "Acute appendicitis."

The postoperative course was uneventful until the third day, when some abdominal distention developed. On June 18, two days later, the distention had become marked, and vomiting began. Aspiration of the contents of the stomach

was performed, and by the next morning the abdomen was soft. From this time on recovery was rapid and uneventful, and the patient was discharged on June 24.

The temperature never exceeded 101 F. after the third postoperative day. From a study of the urinary output no evidence of renal insufficiency was noted even during the period of distention.

Table 2 shows a sudden drop in the white cells together with a marked rise in the percentage of nonfilamented neutrophils on June 19, the fifth postoperative day, when the distention was first beginning to subside. The final count, made on June 21, two days later, showed a return of leukocytosis and a shift of the neutrophils back to the right. On this same day the patient began to menstruate.

Concentrated extract of liver was injected in doses of 3 cc. on three consecutive days beginning June 16 (table 2). It was started three days before the leukocyte drop was first noted.

Second Admission: On November 29, five months after appendectomy, C. L. was readmitted complaining of severe abdominal pain of twelve hours' duration with nausea.

TABLE 2.—*Leukocyte Counts of the Patient in Case 2, First Admission*

Date	White Blood Cell Count	Neutrophils, per Cent	Lymphocytes, per Cent	Monocytes, per Cent	Eosinophils, per Cent	Nonfilamented Neutrophils, per Cent	Comment
6/13	24,000	80	17	3	0	..	Preoperative count
6/15	17,000	91	9	0	0	63	
6/16	18,800	93	6	1	0	53	Injections of extract of liver started
6/17	13,800	84	13	2	1	55	
6/18	.....	..	..	..	..	..	Distention at height
6/19	7,200	68	29	2	1	86	
6/21	14,500	73	25	0	2	66	Menstruation

Physical examination showed evidence of intestinal obstruction, and laparotomy was performed five hours after admission.

At operation a volvulus of the lower part of the ileum was found; there was gangrene in the portion caught in the loop. The gangrenous 2 feet (61 cm.) of ileum was resected; enteroenterostomy was performed, and the wound was closed without drainage.

The next morning there was moderate generalized abdominal distention, and small emeses were frequent. The stomach had to be aspirated repeatedly, as the patient would not permit continual suction. On December 2, three days after operation, the distention began to decrease and by the fourth day had completely subsided. From this time on, progress was uneventful, and the patient was discharged on December 11.

The temperature on admission was 99 F. On the first day after operation it rose to 101.4 F. but never again exceeded 100.6 F. Urinalysis and study of the urinary output revealed no evidence of renal insufficiency either before or after operation.

The two preoperative white blood cell counts were made four hours apart; both showed the expected marked leukocytosis and appropriate differential counts, including the moderate shift to the left of the neutrophils (table 3). Postoperatively, however, there was a sharp drop in the total count together with a marked increase in the percentage of nonfilamented neutrophils associated with the abdominal dis-

tention. On this occasion also the blood picture returned to normal along with the subsidence of the abdominal symptoms and the onset of menstruation.

Injections of extract of liver had again been given prophylactically (table 3) and in the same doses as before.

CASE 3.—I. A., a white woman aged 50 years, was admitted to the Hospital of the Good Shepherd, Syracuse University, on Sept. 11, 1938, complaining of severe abdominal pain of three days' duration.

The past history showed diabetes over a period of nineteen years under good control with small doses of insulin. From 1932 on, there were recurring attacks of gallstone colic until cholecystectomy was performed on Jan. 18, 1936. Two months after the operation, while the patient was still in the hospital, intestinal obstruction developed. At operation, the cecum was found markedly distended owing to a volvulus with adhesions. The obstruction was relieved, and cecostomy was performed with subsequent recovery. Five months later, the patient was readmitted

TABLE 3.—*Leukocyte Counts of the Patient in Case 2, Second Admission*

Date	White Blood Cell Count	Neutrophils, per Cent	Lymphocytes, per Cent	Monocytes, per Cent	Eosinophils, per Cent	Nonfilamented Neutrophils, per Cent	Comment
11/29	21,000	96	3	1	0	38	Preoperative count, 11:30 a.m.
	31,000	93	3	4	0	51	Preoperative count, 3:30 p.m.
11/30	.....	..	..	..	..	..	Injections of extract of liver started
12/ 1	6,700	59	39	1	1	92	Distention at height
12/ 2	7,600	71	29	0	0	77	Menstruation
12/ 3	8,000	66	25	7	1	77	Basophils, 1 per cent
12/ 7	15,400	54	45	1	0	50	

with recurrence of the obstruction, but on this occasion relief followed intubation without surgical intervention.

A third attack of obstruction began suddenly three nights before admission with severe generalized abdominal pain, increasing distention and obstipation. Vomiting began on the morning of admission.

Physical examination revealed an elderly woman in severe pain. The temperature was 99.2 F.; the pulse rate, 90, and the respiration rate, 20. There was marked abdominal distention with generalized tenderness, a large umbilical hernia, and an old scar over the right rectus muscle.

The preoperative leukocyte count was: white blood cells, 3,300; neutrophils, 34 per cent; lymphocytes, 53 per cent; monocytes, 12 per cent; eosinophils, 1 per cent; 94 per cent of the neutrophils were nonfilamented. Preoperative urinalysis revealed no abnormalities, except that many red and white cells were visible microscopically.

At operation, performed several hours after admission, the ascending and transverse portions of the colon were enormously distended from the terminal part of the ileum to the splenic flexure owing to a volvulus of this entire length of bowel. No evidence of infection was present. During the untwisting of the volvulus the ileum was torn, and the fecal contents were spilled. The tear was repaired and enterostomy done.

After operation the patient fared poorly and died on the third day.

Necropsy showed acute peritonitis, acute pericarditis, bilateral hydrothorax and acute and chronic pyelonephritis with some hydronephrosis. There was also perihepatitis, periportal infiltration and some fatty degeneration of the liver.

CASE 4.—A. T., a white man aged 77 years, was admitted to the Syracuse Memorial Hospital on May 31, 1939, complaining of pain in the back on the right side radiating through to the right upper quadrant of the abdomen. This pain had been occurring for one year and had increased in frequency and severity during the previous six weeks.

The past history showed that ten years previously cholecystectomy and appendectomy had been performed but that neither stones nor inflammation of the gallbladder had been found. There had never been jaundice to the patient's knowledge. There was also a history of peptic ulcer with two hospitalizations, nine and seven years before, respectively.

Physical examination revealed an elderly, well preserved man, not acutely ill. The temperature, the pulse rate and the respiration rate were normal. There was a questionable subicteric tint to the scleras, but aside from this and the old abdominal scars, there were no positive findings.

TABLE 4.—*Results of the Examination of the Blood of the Patient in Case 4*

Date	White Blood Cell Count	Neutrophils, per Cent	Lymphocytes and Monocytes, per Cent	Eosinophils, per Cent	Nonfilamented Neutrophils, per Cent	Nonprotein Nitrogen, Mg. per 100 Cc.	Comment
6/ 1	5,700	60	31	9	Under 25	32	Admission
6/ 6	.....	..	..	..	..	..	Operation
6/ 8	.....	..	..	..	..	..	Distention begun
6/ 9	.....	..	..	..	..	109	
6/10	5,700	80	20	0	95	..	Distention at height
6/13	15,000	80	16	4	40	139	Distention subsided
6/22	10,200	74	23	3	27	38	

The preoperative blood count was not unusual except for eosinophilia, the significance of which is not clear (table 4). Examination showed that the urine and the nonprotein nitrogen were normal. The icteric index was 8, and the van den Bergh test had a slight positive indirect reaction.

At operation, performed on June 6, adhesions were noted about the common duct and were freed. No other cause for the symptoms was discovered.

On June 8, the second day after operation, there was some abdominal distention, and two days later this had become marked in spite of the usual decompression procedures. However, on June 11, the distention began to subside and was gone in forty-eight more hours.

During the period of distention there was present not only failure of the usual postoperative leukocytosis and an extreme neutrophilic shift to the left but also marked renal insufficiency, as shown by the high figures for nonprotein nitrogen in the blood (table 4). The urinary output also was significantly diminished, averaging some 300 cc. in twenty-four hours from June 7 through June 10.

The temperature was elevated to a maximum of 102 F. on June 10 and June 11 but returned to normal rapidly thereafter together with the blood picture and, though more slowly, the nonprotein nitrogen.

The patient was discharged on July 20 as improved, and, up to October 1940, when last followed, had continued at work.

COMMENT

In all 4 cases, including the five admissions, a picture of leukocytic exhaustion coincided with marked abdominal distention in the absence of severe infection. Although blood counts were insufficient to prove that the distention always preceded the white cell failure, yet at least in no instance was the significant blood picture found before the distention had reached its height.

In cases 1, 2 (both admissions) and 4, the distention was of the postoperative paralytic type; in case 3, it was mechanical.

In cases 1 and 4, renal insufficiency was associated with the abdominal distention and white cell failure. In cases 2 and 3, however, this was not observed.

Injections of concentrated extract of liver were followed by some elevation of the white blood cell count in case 1, but in neither admission in case 2 did prophylactic injections prevent the exhaustion picture from developing.

In case 2, the onset of menstruation coincided with the subsiding of the abdominal distention and the return of the blood picture to normal in both admissions. This may not be entirely coincidental, but the significance is not clear and will not be discussed.

Of these 4 reported cases only in cases 3 and possibly 4, might it be assumed that a low leukocyte reserve was present all along. In cases 1 and 2 the patients were vigorous young adults with essentially noncontributory past histories.

SIGNIFICANCE OF THE DEGENERATIVE BLOOD PICTURE

The most important question to be answered from these cases is: Since severe infection did not bring about the picture of white blood cell failure, can abdominal distention have been responsible?

Before taking up this question, however, another will be considered: Does the blood picture in the 4 cases reported confirm or contradict the apparent absence of infection?

To answer this, blood smears in 3 of the 4 cases reported here (the blood smears in case 4 were not available) and in 2 similar cases previously reported (cases 6 and 7) [1] were reviewed. The smears selected were those made in each case at the time of the lowest count and the highest nonfilamented neutrophil percentage (table 5, series 1).

These blood counts were compared with those from a second series of cases in which there was similar leukocytic exhaustion (table 5, series 2). In the latter, however, distention, though present, was less marked on the whole, and severe infection was present in an apparently sufficient degree to have overwhelmed the marrow.

The degree of infection or other irritation of the marrow in each case is indicated in table 5 under "Strain on the Marrow." Three hundred cells were counted in each instance, except in smear 10, in which only 200 cells were counted. The usual Schilling differential blood count was made, except that juvenile cells were not separated from the stabs owing to the difficulty in many instances of satisfactorily differentiating them. Under "Myelocytes" both early and late forms are included. Although myelocytes are reported under their own heading, they are included in the neutrophil percentages besides. A few

TABLE 5.—*Comparison of Two Series of Leukocyte Counts*

Smear	Age of Patient, Years	Sex of Patient	White Blood Cell Count	Neutrophils, per Cent	Myelocytes, per Cent	Lymphocytes, per Cent	Monocytes, per Cent	Eosinophils, per Cent	Basophils, per Cent	Nonfilamented Neutrophils, per Cent	Strain on the Marrow
Series 1. Marked Distention; No Severe Infection											
1 (case 6[1])	..	..	3,200	60.7	0	21.0	17.0	0.7	0.7	93	Laparotomy and salpingitis
2 (case 7[1])	..	..	3,500	66.0	0	20.0	13.3	0.7	0	93	Parturition
3 (case 1)	..	..	5,400	65.7	0	19.0	12.3	2.3	0	95	Appendectomy
4 (case 2, first admission)	..	..	7,200	64.3	0	22.3	12.3	1.0	0	93	Appendectomy
5 (case 2, second admission)	..	..	6,700	58.3	0	30.3	9.3	2.0	0	94	Intestinal resection
6 (case 3)	..	..	3,300	34.3	0	53.0	11.7	1.0	0	94	Preoperative volvulus
Series 2. Severe Infection; More or Less Distention											
7.....	67	M	3,600	74.3	5.7	18.3	7.0	0	0.3	98	General peritonitis and carcinoma
8.....	23	F	3,900	91.0	2.3	7.0	2.0	0	0	93	General peritonitis
9.....	75	M	7,000	70.0	4.0	26.3	3.7	0	0	95	General peritonitis
10.....	63	M	2,400	47.0	4.5	52.5	0	0	0.5	98	Lobar pneumonia
11.....	7	M	8,800	82.7	2.3	17.3	0	0	0	95	Bronchopneumonia

unclassified cells and a rare blast form or two were encountered but disregarded. The nonfilamented neutrophil counts are reported in all tables in percentages related to the total of neutrophils and not to the total of cells.

The counts in table 5 were all made by me; they were all made from cover slip preparations except smears 1 and 10, which were made from slide films.

Comparison of the two series of cases in table 5 shows the following differences: As to neutrophils, in series 1 there was a complete lack of neutrophilia (no case with neutrophils over 66 per cent), and there was even actual neutropenia (neutrophils, 34.3 per cent in smear 6); in series 2 there was a wide spread in the neutrophil percentages, the

variations ranging from neutrophilia (neutrophils 91 per cent in smear 8) to neutropenia (neutrophils 47 per cent in smear 10).

The nonfilamented neutrophil count was extremely high in both series, being 93 per cent or more in every instance. Toxic granules (not listed) were found in almost 100 per cent of the neutrophils of both series.

Myelocytes were uniformly absent in series 1 but uniformly present in series 2.

The percentages of lymphocytes did not appear to be distinctive in either series but ranged somewhat higher in series 1, following the lower neutrophil percentages.

The monocyte percentages in series 1 were increased, ranging from 9.3 to 17 per cent. In series 2, they were decreased, ranging from 0 to 7 per cent.

Eosinophils in series 1 were uniformly present; in series 2, uniformly absent.

Thus in series 1 the absence of neutrophilia and myelocytes and the presence of monocytosis and eosinophils confirmed the clinical absence of severe infection; in series 2, the almost uniformly opposite findings, especially with regard to myelocytes, monocytes and eosinophils, confirmed the presence of infection.

Low total white blood cell counts with marked neutrophilic shift to the left were found in both series (table 5). In the cases of series 1, this would seem to contradict the indications of the other blood findings with regard to the absence of any severe infection, since leukopenia and high percentages of nonfilamented neutrophils are usually thought of as associated with marrow failing from overwhelming irritation. Schilling,[2] however, has shown that the shift to the left and the falling total count are not always due to collapse of the hemopoietic cells from overwork but may be the result of a "degenerative inhibition of development." The ordinary neutrophilic shift to the left, due to simple stimulation (as in pyogenic infections) with the eventual output of juvenile cells and myelocytes as the stimulus increases, he called regenerative; the other type of shift to the left, which is due to actual inhibition in development resulting in the output of stab neutrophils without young forms, he called degenerative. The regenerative and the degenerative neutrophilic shift are thus qualitatively distinct and not merely the results of different degrees of the same stimulation.

With the regenerative shift, leukocytosis is the rule; with the degenerative shift, decrease in total counts to the point of leukopenia

2. Schilling, V.: The Blood Picture and Its Clinical Significance, St. Louis C. V. Mosby Company, 1929, pp. 146-154 and 244.

occurs. It seems generally accepted that a decreasing total count may also accompany a regenerative shift in the presence of continued severe infection as the result of overstimulation with exhaustion of the marrow. In what number of these instances, however, the leukocyte drop is in reality due to a degenerative influence cannot be estimated as yet.

Moderate and even marked degrees of neutrophilic shift to the left may result from stimulation alone (regenerative shift), but when the shift is extreme, with over 80 and even 90 per cent of the neutrophils nonfilamented, this is undoubtedly due to the inhibitory influence (degenerative shift).

Naegeli [3] also recognized the degenerative stab, pointing out that "toxic influences may interrupt the maturation of the cells [the neutrophils] and cause such changes in their structure as to prevent any accurate estimation of their age by Arneth's method." For this reason I have preferred to use the expression "shift to the left" rather than "immature" in speaking of the neutrophilic stab. "Shift to the left" means no more than it says, while "immature" as a description of the degenerative stab appears to tell only part of the story.

The low counts and the extreme shifts to the left in series 1 (table 5) represent degenerative qualities, then, and do not contradict the evidence of the rest of the count that no severe infection is present. Moreover, the occurrence of these same qualities in series 2 (table 5) indicates that a degenerative influence exists along with the regenerative, i. e., that in these cases there is a mixed degenerative-regenerative picture.

Schilling [2] did not state in so many words that the degenerative blood picture could occur in the total absence of infection or even that it could exist in a pure form, i. e., without regenerative elements. In his remarks on prognosis, however, he does describe a blood picture similar to those in the cases in series 1 (table 5) in which the prognosis is "not unfavorable" and in which no regenerative elements are present. His words are as follows: "Subnormal counts with degenerative shift of the neutrophils, lymphocytosis, monocytosis and presence of eosinophils per se are not unfavorable." Of the 5 patients in series 1 (pure degenerative picture) only 2 died; of the 5 in series 2 (mixed degenerative-regenerative picture) all died.

Thus the answer to the question of whether or not the blood picture in the 4 cases reported actually confirmed the clinical absence of severe infection is in the affirmative.

3. Naegeli, K., cited by Musser, J. H., and Wintrobe, M. W., in Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1921, vol. 6, p. 739.

ROLE OF ABDOMINAL DISTENTION IN THE PRODUCTION OF THE DEGENERATIVE BLOOD PICTURE

I shall return now to the first question, which was in substance: Can the distended intestine in the 4 cases reported here and in the 2 previously reported (cases 6 and 7) [1] have been the cause of the associated degenerative blood picture?

In these 6 cases (comprising 7 admissions), abdominal distention was of the postoperative paralytic type in all but 1, and the involvement apparently included the colon in every instance. Accordingly, a further study of the blood picture occurring with distention was directed toward mechanical obstructions and those occurring at or above the level of the ileocecal valve. Recent cases of this type were reviewed from the records of the Hospital of the Good Shepherd, Syracuse University, and the Syracuse Memorial Hospital. Other criteria of selection were the presence of abdominal distention, complete obstruction as proved by operation, adequate preoperative blood counts and the absence of complicating factors, such as infection and gangrene, at the time of the counts.

The first 20 cases in which these requirements were fulfilled were used. The causes of the obstruction were: adhesions in 12 cases; intussusception in 3 cases; hernia in 2 cases, and volvulus, Meckel's diverticulum and gastroenterostomy, each in 1 case. The levels of obstruction varied as follows: the jejunum in 2 cases; the upper part of the ileum, 2 cases; the lower part of the ileum in 11 cases; and the terminal part of the ileum in 5 cases. The obstructions had been present for periods of one-half day to five days before hospitalization; i. e., before the first blood count.

In 5 of the 20 cases the blood picture showed unmistakably degenerative tendencies. (In the other 15, these tendencies were not apparent.) In 4 of the 5, the total white blood cell count was low, and the shift to the left was marked. In the fifth, in which two preoperative counts were reported, the degenerative tendency was evidenced by the increased shift to the left and the decreased percentages of neutrophils in the second count as compared with the first, though the original leukocytosis persisted.

The duration and the level of the obstruction may be important factors in determining the onset of the degenerative changes, though in my small series this cannot be demonstrated. Such a possibility is apparently considered by Demidova,[4] who found in a study of the white blood cell count in cases of acute ileus that in the group in which "toxic"

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4. Demidova, P. N.: Blood Picture in Acute Ileus, Vestnik khir. **56**:356 (Sept.-Oct.) 1938; abstracted, J. A. M. A. **112**:1775 (April 29) 1939.

obstruction was noted of the small intestine leukocytosis was soon replaced by leukopenia.

Thus the degenerative blood picture may occur with distention of the small as well as with distention of the large intestine and with mechanical obstruction as well as with paralysis, and still without evidence of any complicating infection or necrosis.

These findings go still farther in confirming abdominal distention itself as the cause of degenerative changes in the blood picture. The actual mechanism must be in the inhibiting of the hemopoietic function of the marrow by some toxic substance, apparently nonbacterial in origin and possibly absorbed from the distended intestine. The effect of the hypothetic substance on leukopoiesis is purely inhibitory and not due to overstimulation such as is supposed to occur at times from overwhelming infection.

TABLE 6.—*Leukocyte Counts of Patients with Uncomplicated Mechanical Abdominal Obstruction*

Patient	Sex	Age, Yr.	White Blood Cell Count	Neutrophils, per Cent	Lymphocytes, per Cent	Monocytes, per Cent	Eosinophils, per Cent	Nonfilamented Neutrophils, per Cent	Duration of Obstruction, Days	Level of Obstruction
1	M	58	5,200	55	37	8	0	87	4	Lower part of ileum
2	F	49	5,700	81	16	3	0	86	2	Terminal part of ileum
3	F	60	6,600	51	45	4	0	64	5	Lower part of ileum
4	M	60	7,300	83	——16——		1	55	3	Upper part of ileum
5	M	22	21,000	94	4	2	0	42	1	Lower part of ileum
			18,000	44	44	11	1	88	2	

But what of abdominal distention that is secondary to pyogenic infection? Can degenerative influences also develop from this, and if so, can they be distinguished from the regenerative influences originally present?

Illustrations of this situation are found in the 5 cases of series 2 (table 5). In the first 3 cases there was general peritonitis; in the last 2, bilateral pneumonia. The blood pictures were all of the mixed degenerative-regenerative type already mentioned and both degenerative and regenerative influences could be distinguished. The regenerative elements consisted of neutrophilia (when present), presence of myelocytes and lack of eosinophils; the degenerative, of low total white blood cell count, normal neutrophil percentage or actual neutropenia (when present) and extremeness of the neutrophilic shift to the left. Even though pyogenic infection was the primary disorder in these 5 mixed cases, the degenerative elements might well have been the result of secondarily developing abdominal distention and not of overwhelming of the marrow.

The consideration of abdominal distention as at least a contributing cause of white blood cell failure in cases of pneumonia is of especial interest and deserves more discussion than can be given here. It may be said, however, that whenever the degenerative tendency appears with pneumonia (as, for that matter, with any infection, whether intra-abdominal or extra-abdominal), associated paralytic intestinal distention should always be looked for.

DEGENERATIVE BLOOD PICTURE OF GASTROINTESTINAL TRACT INVOLVEMENT OTHER THAN ABDOMINAL DISTENTION

There is one other type of condition showing the degenerative blood picture that deserves consideration here. This is the condition in which the gastrointestinal tract is diseased but in which abdominal distention is not an outstanding characteristic. Examples of this are typhoid (as is well known),[2] certain epidemic forms of bacillary dysentery [5] and, frequently idiopathic ulcerative colitis.[6] With all these conditions the degenerative characteristics of the blood picture are striking. Although abdominal distention may not be clinically present, it is not difficult to imagine that in these instances in some way the same toxic absorption is taking place as in cases in which distention is actually demonstrable. However, whether the absorption is due to a subclinical distention or to the involvement of the intestinal wall by bacteria or ulceration is not known.

It is altogether possible, of course, that the inhibiting substance is formed indirectly by some intermediate organ as, for example, the liver. The sequence of events would then be: (1) absorption of toxic products from the wall of the intestine (either distended or involved in some other way); (2) damage to the liver by the toxins with disturbance of liver function, and (3) production of a second toxic substance, the actual leukopoiesis-inhibiting one, by the damaged liver. Theoretically, then, the liver might under certain conditions be capable of forming the inhibiting substance directly, i. e., in the absence of any gastrointestinal disease whatever.

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5. Ginsburg, H. M.; Hirschberg, E. M., and Brisker, F.: Bacillary Dysentery: A Preliminary Report Stressing the Blood Picture, J. A. M. A. **113**:1321 (Sept. 30) 1939.

6. Moltke, O.: Number and Percental Apportionment of White Blood Corpuscles in Suppurative Coloproctitis, Bibliot. f. læger **128**:83 (April) 1936; abstracted, J. A. M. A. **107**:172 (July 11) 1936. Garvin, R. O., and Bargen, J. A.: The Hematologic Picture in Chronic Ulcerative Colitis: Its Relation to Prognosis and Treatment, Am. J. M. Sc. **193**:744 (June) 1937. Vickers, P. M., and Bargen, J. A.: An Index of Prognosis in Thrombo-Ulcerative Colitis, Proc. Staff Meet., Mayo Clin. **13**:408 (June 29) 1938.

It should be understood that I am not attempting to show that all types of leukopenia are due to the inhibiting action of some hypothetic toxic substance. Obviously, those of agranulocytosis, aleukemic leukemia and aplastic anemia are of fundamentally different natures from that of the degenerative blood picture. I have sought only to bring out that at least one type of leukopenia, the one characterized by the degenerative shift, appears to be the result in certain instances of intestinal distention. Perhaps, however, the origin of degenerative leukopenia in many other conditions, such as influenza, kala-azar and pappataci fever,[2] will eventually be found explainable on the basis of the same hypothesis as to the formation of the inhibiting substance.

Kaufman and vom Saal [7] recently published an article on the white blood cell counts of patients with various intra-abdominal diseases. They found that a marked neutrophilic shift to the left may occur "in all types of acute peritoneal irritation, even without infection." This depends on "sudden peritoneal shock or irritation" and is "probably due to inflammation of a chemical nature."

Whatever may ultimately prove to be the cause of the degenerative blood picture, whether abdominal distention, peritoneal irritation or some other factor, the observation of Kaufman and vom Saal that a marked neutrophilic shift to the left may occur even without infection is of great importance and is fully confirmed by my observations. It means, for instance, that an abnormally high or increasing nonfilamented neutrophil count is no longer to be taken as an inevitable indication of the onset, the spread or even the presence of infection. Such a count may, for example, be merely the result of temporary postoperative distention.

A study of the white blood cell picture in cases of leukocytic exhaustion with regard to its degenerative and regenerative qualities, then, may be of great value to the surgeon since the question as to the presence or absence of infection in a given case, which may sometimes be vital, may also at times be answerable by this procedure.

SUMMARY AND CONCLUSIONS

Four cases are reported and 2 cited from a previous article; all illustrate the association of leukocytic exhaustion with abdominal distention in the absence of severe infection. The blood picture in these cases in which there is no severe infection is compared with cases showing a similar white blood cell failure, but in which severe infection is present. In the former the blood picture is purely degenerative; in the latter, mixed degenerative-regenerative.

7. Kaufman, R. E., and vom Saal, F.: Leukocyte Changes in Acute Peritoneal Irritation, J. Lab. & Clin. Med. **26**:468 (Dec.) 1940.

The pure degenerative blood picture is characterized by: low to leukopenic white blood cell counts, normal to neutropenic neutrophil percentages, absence of myelocytes, normal to increased percentages of lymphocytes and monocytes and presence of eosinophils. In the mixed degenerative-regenerative picture, regenerative elements are found, such as neutrophilia, presence of myelocytes, monocytopenia and absence of eosinophils.

The prognosis in cases of leukocytic exhaustion with pure degenerative shift is "not unfavorable" (Schilling [2]); however, with mixed degenerative-regenerative shift the condition is fatal.

In a series of cases of uncomplicated mechanical obstruction of the small intestine with distention, in 5 out of 20 the degenerative tendency was present. In 5 cases of peritonitis and pneumonia in which there was leukocytic exhaustion with mixed degenerative-regenerative shift, the degenerative elements were distinguishable from the regenerative. Abdominal distention was present in all 5 cases.

The degenerative type of white blood cell failure may also be found with disease of the gastrointestinal tract other than that associated with obvious abdominal distention. Examples of this type of disease are typhoid and certain types of dysentery and colitis.

Abdominal distention is concluded to be at least one important cause of the degenerative blood picture. The actual mechanism of production is through absorption from the distended intestinal wall of some apparently nonbacterial toxic substance which acts either directly or indirectly as an inhibitor of leukopoiesis.

Thus, a low or falling white blood cell count with marked neutrophilic shift to the left and toxic granulations does not necessarily mean that the marrow is overwhelmed by infection, that the patient's resistance is abnormally low or that the prognosis is bad; it may be due to a purely degenerative influence.

A fuller study of the white blood cell picture is urged in all cases of leukocytic exhaustion, particularly if the question as to the presence or absence of infection is important.

Drs. E. S. Van Duyn and T. L. Bryant's cases are reported with their permission; blood smears were lent by Dr. E. G. Allen; the staffs of the library of the Syracuse University College of Medicine and the record rooms of the Hospital of the Good Shepherd, Syracuse University, and the Syracuse Memorial Hospital cooperated in the preparation of this study.

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INCIDENCE OF MALIGNANT GROWTH OF THE UNDESCENDED TESTICLE

A CRITICAL AND STATISTICAL STUDY

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Whether the undescended testicle is more liable to become the seat of malignant change than the scrotal testicle and whether, of undescended testicles, the inguinal is more likely to be affected than the abdominal are two questions which have not been satisfactorily answered. In 1927 Wangensteen wrote, "No greater diversity of opinion probably exists concerning anything in medicine than the question of malignancy in the undescended testis." In 1936 Hinman said, "Whether tumor is relatively more frequent with inguinal than with abdominal retention is uncertain."

From the data recorded in the literature it can now be stated unequivocally that the undescended testicle is more liable to malignant change than the normally placed testicle and that the abdominal testicle is more liable to malignant change than the inguinal.

There are at least six main reasons why these truths have so long remained obscure: 1. The medical profession has neglected the science of statistics; it has tried to draw conclusions from figures without knowing how to manage them. 2. Medical authors have committed almost incredible errors of misquotation. 3. Differing definitions of the words "cryptorchidism," "cryptorchid," "ectopy," "anorchidism" and "monorchidism" have led several authors to false conclusions. 4. Authors have tended to publish statistics from their hospital practice and to neglect the implication of the figures from their private practice. 5. During the early years of discussion of malignant growth in the undescended testicle, preceding and following Johnson's first recorded case of malignant growth in the abdominal testicle in 1859, the number of reported cases of malignant growth in the inguinal testicle greatly exceeded that of cases of malignant change in the abdominal testicle. That disproportion no longer exists, probably because the abdomen is

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much more frequently explored than in those years. Yet those early figures are still extensively quoted and continue to create an erroneous impression. 6. The incidence of malignant change in the undescended testicle has been computed in terms of the number of patients. If the incidence is computed in terms of the number of testicles, the cases of malignant change in bilateral undescended testicle achieve their true significance.

STATISTICAL AND HISTORICAL REVIEW

The Science of Statistics.—Opinion concerning the probability of malignant change in the testicle has varied from decade to decade largely because physicians have not been aware of the theories of chance variation and have not tested their conclusions by criteria based soundly on the science of statistics. It is the duty of physicians who attempt to draw conclusions from statistics to become acquainted with the statistical method. Otherwise, erroneous conclusions will probably result. The writings of Fortuyn were instrumental in introducing me to the subject of statistics, and they still remain the simplest and shortest presentation. The writings of Hill in the *Lancet* have been published in book form and constitute the best approach for the busy practitioner. The articles were written for physicians and deserve widespread reading in America. It is to be hoped that eventually every medical student will be taught a working knowledge of the statistical method.

Not the least essential part of the statistical method is the assemblage of data. The data as recorded in the literature on the undescended testicle leave much to be desired. For example, there is the matter of the meaning of "hospital admissions." It is a fact that many patients are readmitted and hence in a table of "hospital admissions" are counted again and again. In one hospital it is estimated that 50 per cent of the total admissions are readmissions. In another hospital 1 patient was readmitted thirteen times in one year, and it was estimated that between 15 and 20 per cent of the total admissions were readmissions. If medical writers are to deal with figures, they must persuade hospital administrators to adopt a different system of recording than is now employed in most hospitals.

In this regard is the matter of sex. Many hospitals do not record the numbers of male and female patients. It is often assumed that about half are male and half female, but an active gynecologic service will cause this proportion to vary considerably. The sex incidence of disease does not greatly interest most writers, but in considering a subject of the sort dealt with here an accurate idea of the number of male patients observed becomes important.

One of the most disappointing features of this study was the large number of writers who did not tell the proportion of abdominal and of

inguinal testicles among undescended testicles in which there was no malignant growth. They give the number of patients with undescended testicle but give no indication of how many had bilateral nondescent or how many had nondescent of testicles in the various locations. While it has been possible to collect a sufficient number of papers giving these details to render conclusions drawn from them statistically sound, the task might have been much easier and the figures much larger if all the writers on the subject had given all the data.

Misquotations.—The subject of malignant growth in the testicle contains many inherent complexities; it is confusing without the complications of misquotation.

The most startling example of misquotation in recent years was the misinterpretation by Hinman, a recognized authority, of a statement by Coley, an outstanding authority of two decades ago. In 1915 Coley wrote:

> . . . At the Hospital for Ruptured and Crippled, from 1890-1907, in 59,235 cases of inguinal hernia in the male sex there were found 737 cases of undescended testis, without a single case of sarcoma of the undescended testis.

In 1924 Hinman wrote:

> . . . Coley, for instance, in 59,235 cases of inguinal hernia, in the Hospital for Ruptured and Crippled Children, from 1890-1907, encountered malignancy of the undescended testicle 737 times—1 in every 80—an unbelievably high incidence . . .

Less startling but more far reaching, for it has been widely repeated, is the following instance of misquotation. In 1913 Bulkley wrote:

> . . . Thus in 182,729 male admissions to general hospitals, there were 3 cases of malignant growths of intra-abdominal testicles, or about 1 in each 60,000 cases.

In 1924 Hinman, basing his figures on those of Bulkley, said:

> . . . About 1 in every 1500 male admissions has teratoma as compared to 1 malignant abdominal cryptorchid in every 60,000 admissions of cryptorchid . . .

This statement was used by MacKenzie and Ratner to fortify their thesis that the abdominal testicle undergoes malignant change less frequently than the inguinal.

A frequently quoted misquotation is that by Coley of a statement of Bulkley. In 1913 Bulkley wrote:

> . . . My statistics from the Presbyterian Hospital show 2 cases of malignant abdominal and no cases of malignant inguinal testes.

In 1915 Coley wrote:

> . . . Bulkley, himself, however, found at the Presbyterian Hospital 2 cases of malignant abdominal in 12 cases of malignant inguinal testes.

Perhaps the most widely circulated error of quotation occurred early in the literature on this subject. In 1869 Schaedel wrote, as his graduation thesis in medicine, "Ueber Kryptorchidie." In his remarks about malignant growth in the testicle he wrote:

> . . . Während in den Jahren 1853-1859 in den grössten Londoner Spitälern 36 Carcinome normaler descendirter Hoden behandelt wurden, kamen in demselben Zeitraume in den nämlichen Spitälern 5 Carcinome retinirter Hoden zur Operation. (During the years 1853-1859, 36 carcinomas in normally descended testes were treated in the largest London hospitals; in the same period 5 carcinomas in retained testes came to operation in the same hospitals.)

In 1887 von Kahlden quoted Schaedel and mistakenly gave the period as 1853 to 1854. In practically every compilation of statistics since that time these figures have occurred, the series being attributed to von Kahlden more often than to Schaedel. Not long after, another writer, quoting this statement from von Kahlden (few give evidence of having consulted Schaedel in the original), interpreted the figures as coming from a large London hospital. In this doubly erroneous form the passage has been widely quoted, and much space has been used in repudiating the possibility that such a large number of cases could have come from any hospital in one year.

In a copy of Schaedel's dissertation obtained from the Library of Congress no reference was found for the aforementioned statement. Schaedel cited (with an incomplete reference) a case reported by Mr. Partridge. This case was 1 of 36 collected by the editors of the *Medical Times and Gazette* from the pages of that publication for the six years preceding the report in September 1859. These must be the 36 cases to which Schaedel referred. They were from eleven of the well known London hospitals together with nine of the provincial hospitals. No reference could be found for the 5 cases of carcinoma of the retained testis said by Schaedel to have come to operation during the same period. Only 2 cases of malignant growth in the undescended testicle could be found in the literature for the period 1853 to 1859, and in only 1 of these was operation performed. In Spry's case the patient was operated on and recovered. He wrote:

> . . . It appears that the only two cases of excision of diseased testes, retained in the groin, performed in this country, are those recorded by Mr. Arnott, of the Middlesex Hospital (1845), and by Mr. Storks of Gower-street (1847).

In Johnson's case operation was not performed. At autopsy a malignant condition of the abdominal testicle was found. This is probably the first recorded case of malignant change in the abdominal testicle. In his book on diseases of the testis Curling wrote:

> . . . There are many cases on record of carcinoma affecting testicles retained in the groin.

Later in the book he wrote:

> . . . The excision of a testicle detained in the groin and affected with malignant disease has been performed by Arnott of the Middlesex Hospital (1845) and Storks of Gower-street (1847), Spry of Truro (1857) and Fayrer of Calcutta (1857).

Another editorial report of the *Medical Times and Gazette* lists 6 cases of cystic sarcoma of the testicle occurring during the same period, 3 in London and 3 in the provinces. In all 6 cases the involved testis was normally descended.

Definition of Terms.—Different definitions of "cryptorchidism" and related terms have been the source of much confusion and some actual error. Some consider "cryptorchidism" to mean bilateral abdominal retention; this might be the literal meaning. Most writers use the term to refer to any degree of incomplete descent in one or both testicles. This usage is in accord with Webster's "New International Dictionary of the English Language," in which "cryptorchidism" is defined as signifying "a condition in which the testes fail to descend normally"; and "cryptorchid," as signifying "one affected with cryptorchidism." Many physicians consider a cryptorchid to be an undescended testicle. According to Stedman's "A Practical Medical Dictionary," a cryptorchid is "one whose testes have not descended into the scrotum." The aforementioned dictionaries will be followed in the use of these terms. "Ectopy" is used by some as synonymous with "cryptorchidism"; by others it is used in relation to perineal, penile and femoral locations. It will be used in the latter sense, that is, as designating a type or subdivision of cryptorchidism.

Confusion likewise has arisen from the loose use of "monorchidism" and "anorchidism." The former should not be used to mean unilateral abdominal retention; nor should the latter be used for bilateral abdominal retention. The terms should be used as indicating that the patient actually has either one or no testicles, as the case may be. As congenital defects, monorchidism and anorchidism are extremely rare; more often such states are acquired. There will be no occasion to use these terms. In this paper I shall use the following classification:

Cryptorchidism: A. Maldescent or nondescent: abdominal, inguinal, superficial inguinal, pubic, high scrotal. B. Ectopy: perineal, penile, femoral.

In my interpretation of the literature, a testicle at the internal ring is considered abdominal, and one at the external ring or protruding from the external ring is considered inguinal. "Superficial inguinal" refers to the type of testis which is found at operation to have made its exit from the external ring and then passed superficial to the external oblique muscle of the abdomen for varying distances toward the anterior superior spine of the ilium, coming to lie between the superficial fatty

layer and the aponeurosis of the external oblique muscle. In the German literature this is known as the preinguinal location. I am aware that the superficial inguinal cryptorchidism may logically be, and sometimes is, classed as ectopy. "Pubic" refers to the testicle which has escaped from the external ring and has not passed low enough into the scrotum to escape pressure between an external force and the pubic bone. "High scrotal" is self explanatory. Since any tumor developing in a high scrotal testicle could hardly be distinguished from one arising in a normally descended testicle and since the effects of external violence would rarely compress such a testicle against the pubic bone, a high scrotal testicle will be considered as normal in this discussion. For practical purposes superficial inguinal cryptorchidism will be grouped together with inguinal cryptorchidism proper. No report was found in which a malignant growth in an inguinal testis was described as being superficial to the external oblique muscle of the abdomen. Undoubtedly such cases have occurred; it would seem that the surgeon could easily distinguish whether the external oblique muscle lay over or below the tumor, but so far as I know, this detail has not been published in the papers on malignant change in the inguinal testicle.

Bulkley was one of the writers who felt that the abdominal testis did not often undergo malignant change. He stated that malignant growth occurred in about 1 abdominal testis in 75. He calculated as follows: In the literature he found (as stated earlier) records of 182,729 male patients with 3 cases of malignant growth in the abdominal testicle, that is, about 1 to 60,000. Then he quoted the figures of Marshall (from Koenig) and those of Rennes (from Monod and Terillon). The former found 12 cryptorchids among 10,800 recruits and the latter 6 among 3,600; together, these results made a total of 18 to 14,400, or 1 to 800. The figure 60,000 divided by 800 gave a quotient of 75. However, there is no evidence that Marshall and Rennes were referring to abdominal retention; hence the two sets of figures do not admit of comparison.

I have obtained photostatic copies of several pages (82, 83, 207) of Marshall's book. He wrote:

> . . . In some individuals both testicles are not in the scrotum. During the examination of 10,800 recruits, I found five in whom the right, and six in whom the left, testicle was not apparent. I have met with only one instance where both testicles had not descended.

This is not clearcut, but it is doubtful whether one is entitled to conclude that all these were cases of abdominal retention. Koenig quoted Marshall as follows:

> Bei Erwachsenen fand Marshall unter 10800 Recruten Kryptorchismus 1 mal, Monorchismus 5 mal rechts und 6 mal links. (Among 10,800 adult recruits,

Marshall found cryptorchidism once, monorchidism five times on the right and six times on the left.)

Bulkley interpreted *Kryptorchismus* and *Monorchismus* as meaning abdominal retention and wrote:

. . . We must conclude, therefore, that the abdominally situated testicle is relatively immune to malignant changes.

This is an outstanding example of a widely quoted error arising from differing definitions.

Hospital Incidence Versus Private Practice Incidence.—In several instances, authors have drawn conclusions from but a part of their total experience. They have given figures for their hospital experience and neglected to give comparable figures for their private cases. Thus, several writers have seen more cases of testicular cancer in their private practice than in their hospital series. They have told how many patients were admitted to the hospital but not how many patients were observed in their private practice. Often the hospital is a specialized institution, yet the figures obtained there are offered with the implication that they represent a cross section of the entire population. A more representative figure would probably emerge from the private series. In any event, the entire experience of the writer should be offered rather than just a segment.

For example, almost every writer quotes Eccles, Kocher and Coley. Eccles saw 854 undescended testes with no malignant growths; in 1919 Coley reported 1,357 with no malignant growths; Kocher saw 1,000, in 1 of which there was malignant change. Together these men recorded 3,211 undescended testicles, in only 1 of which there was a malignant process. Of the 3,646 cases of undescended testes assembled by Hinman in 1936, these three reports contributed the great majority. Yet Coley elsewhere in his paper records 12 undescended testes in a total of 64 cases of sarcoma of the testis. Eccles mentions that in 1 of 40 cases of sarcoma the growth was in an abdominal testicle. It can readily be imagined that Kocher in his long career as a surgeon saw more than 1 case of malignant growth in an undescended testicle. It is misleading to accept one series and not the other. Probably these three much quoted but essentially misleading series should be dicarded if one is to obtain an accurate idea of the facts.

Neglect to Indicate in Which Cases the Condition Was Bilateral.—Since failure of descent may affect either one or both testes and since malignant degeneration also may be unilateral or bilateral, more informative figures are gained by multiplying the number of patients by 2, for then the cases in which the condition was bilateral achieve their true significance.

STATISTICS

As a preliminary step in the study of the incidence of malignant growth in undescended testicles, it was necessary to learn how frequently nondescent or partial descent occurred. Several writers have referred to the figures obtained from examination of the Austrian army (1887) and of the American drafted army (1917 and 1918). Gilbert and Hamilton furnished some of the tables on which their figures were based. One of these is given in table 1 with the addition of the figures of Rennes. The resultant figure for incidence, 0.23 per cent, seems to be as accurate a figure as can be obtained. It is lower than the figure based on hospital admissions; this shows once again that the population of a general hospital is not typical of the entire population. It may be concluded that about 2 men in 1,000 have maldescent of the testicle and that 1 of about every 500 men is a cryptorchid.

TABLE 1.—*Incidence of Nondescent of Testicle in Army Recruits*

Author	Recruits Examined	Source	Recruits with Nondescent	
			Number	Per Cent
Marshall (1828)	10,800	British and French armies	12	0.102
Rennes (1831)	3,600	French army	6	0.16
Myrdacz (1887)	6,962,543	Austrian army (1870-1882)	14,057	0.2
Love and Davenport (1920)	2,754,154	American drafted army (1917-1918)	8,538	0.31
Southam and Cooper (1927)	10,000	Scottish recruits (1916-1917)	52	0.5
Total	9,741,097		22,665	
Average				0.23

A figure which has shown but little variation through the years is the percentage of those with some degree of maldescent who have malignant growth in the testicle. This figure ranges from 7.5 to 15; in the series shown in table 2 it is 7.8. I have collected 1,422 cases of testicular malignant growth from the literature; 165 (11.6 per cent) of the patients were cryptorchids. Gilbert and Hamilton amassed over 7,000 cases of tumor, and 840 (over 11 per cent) of the patients were cryptorchids. The difference between 0.23 ± 0.0015 per cent (table 1) and 11.0 ± 0.3 per cent is so significant that it may be concluded without fear of controversion that the malignant process is more likely to affect the maldescended organ.

To approach this from another aspect, I collected from the literature reports on 1,413 patients with undescended testicles (table 3); in 22 of these maldescent was associated with malignant change in the testicle. In some reports it is not clear how many testicles were involved; in some cases the condition was undoubtedly bilateral. The incidence of malignant change was found to be 1.5 ± 0.3 per cent—much higher than is gen-

erally concluded from collected series. This is because the large and misleading series of Eccles, Coley and Kocher have been excluded. Of the 500,000 patients in table 2, malignant degeneration of the scrotal testicle occurred in 362, an incidence of 0.07 ± 0.003 per cent. The difference between 1.5 ± 0.3 and 0.07 ± 0.003 is 1.43 ± 0.32 per cent. This difference, which is more than four times its standard error, confirms the conclusion that the undescended testicle is more liable to be affected by malignant change.[1] I hasten to add that this does not prove that the malposition caused the malignant change. It merely indicates that the difference is greater than one would expect from chance and that thus there is some causal agent operating. It is likely that

TABLE 2.—*Incidence of Malignant Testicular Tumor*

Author and Date	Admissions of Male Patients	Malignant Testicular Tumors			
		Total Number	Scrotal	Abdominal	Inguinal
Eccles (1903)	84,000	40	39	1	0
Howard (1907)	110,000	65*	56	0	8
Coley (1908)	59,000	34	31	3	0
Bulkley (1913)	13,000	13	11	2	0
Southam and Linell (1923)	57,000	38	34	3	1
MacKenzie and Ratner (1934)	65,000	26	23	1	2
Hinman and Benteen (1936)	39,000	40	37	3	0
Christofferson and Owen (1940)	28,000†	119	114	0	5
Campbell (1942)	50,000†	19	17	1	1
	505,000	394	362	14	17
Percentage of 500,000		.078	.072		
Percentage of 394			91.8	3.5	4.3
				7.8	
Percentage of 31				45	55

* In 1 of the patients the "retained" testis was "just below the external ring."
† This figure represents an estimation of the number of patients admitted.

the same factor which caused the failure of descent also causes the malignant degeneration. More and more cases are being recorded of malignant change occurring in testes which have been placed in the scrotum. Eventually, statistical analysis of these cases may throw some light on the malignant process in general. From among the 500,000 male patients admitted to the hospitals there were 14 with malignant growth in the abdominal testicle and 17 with malignant growth in the inguinal testicle. In an exhaustive survey, Gilbert and Hamilton found records of 345 cases of malignant growth in the abdominal testicle and 490 cases of malignant growth in the inguinal testicle. The percentages are almost identical, 45 and 55 in my series, and 41.3 and 58.7 in theirs.

1. It should be stated that if the incidence is computed on the basis of number of testicles, a figure of even greater statistical significance is obtained. Not more than 20 per cent of the patients with undescended testicles had bilateral nondescent, while almost all of the 500,000 patients had bilateral descent.

The incidence shown in table 3 is much larger than that generally reported from collected series. I believe that this is because the often quoted series of Eccles, Coley and Kocher are essentially misleading; they have therefore been excluded. Approximately the same incidence (1 to 50) is obtained from calculations with the figures in table 6 and confirms the major conclusion arrived at by another approach from the data in table 2, that is, that the undescended testicle is much more liable to malignant change than the normally placed organ. Thus by three different approaches the same conclusion is obtained. The confusion of former years disappears.

TABLE 3.—*Incidence of Malignant Growth in Nondescended Testicle*

Author	Patients with Undescended Testicles	Patients with Malignant Growth in Undescended Testicles
MacKenzie and Ratner	105*	3
Hinman and Benteen	155	3
Southam and Linnell	413	4
Hoffstatter	181	4
Keyes (in discussion on Cunningham)	40	0
Thiessen and Walters	96	0
Counseller	113	0
Owen	20	5
Campbell	158	2
Brenner	75	0
Goritz	57	1
	1,413	22
Ratio		1:64
Percentage		1.5

* This figure is taken from the paper covering a ten year period. The 3 patients with malignant growth in the undescended testicles were encountered in the succeeding three years and hence the actual period covered is thirteen years. Thus the figure of 105 (about 10 per year) should be expanded to about 135. This would make no great difference in the incidence, however, and would not alter the conclusions reached.

Table 4 comprises all the reports I could find (except one or two papers in which the protocols were too meager) which offered figures to show the relative incidence of abdominal and inguinal maldescent. Abdominal maldescent accounts for 14.3 per cent of all the cases. The difference between 41.3 ± 1.7 per cent (from Gilbert and Hamilton's series of cases of malignant growth in the undescended testicle) and 14.3 ± 0.7 per cent is 27 ± 1.8 per cent, a figure which is fifteen times its standard error and therefore of enormous statistical significance. Gilbert and Hamilton stress the point, and I am inclined to agree, that most authors consider as abdominal a certain number of testicles which migrate back and forth between the abdomen and the inguinal canal and which are therefore properly to be considered inguinal. If Gilbert

and Hamilton's percentage of 10.8 is more nearly correct, then the susceptibility of the abdominal testicle to malignant change is even more marked than I have indicated.

There are those who may believe that a collective review does not give the actual comparative incidence of malignant change in the inguinal

TABLE 4.—*Relative Incidence of Abdominal and Inguinal Nondescent of Testicle*

Author and Date	Undescended Testicles				
	Total Number	Inguinal	Superficial Inguinal	Pubic	Abdominal
Bryant (1867)	7	4	..	...	3
Eccles (1903)	727	334	..	254	139
Odiorne and Simmons (1904)	87	51	1	18	17
Burdick and Coley (1926)	197	83	73	24	17
Brunzema (1929)	132	122	7	..	3
Frühman and Sternberg (1930)	192	87	77	..	28
Heinecke (1932)	30	21	9	..	0
Counseller (1933)	102	71	..	..	31
Thiessen and Walters (1935)	96	43	..	35	18
Bjerre (1935)	350	340	..	..	10
Wangensteen (1935)	23	20	..	..	3
Campbell (1942)	176	85	46	12	33
Total	2,119	1,261	213	343	302
Percentage		59.3	10.0	16.4	14.3

TABLE 5.—*Proportion of Cases of Malignant Growth in Abdominal and in Inguinal Testicles in the Same Hospital*

Author	Cases of Testicular Malignant Growth	Cases of Malignant Growth in		
		Undescended Testicle	Abdominal Testicle	Inguinal Testicle
Authors in table 2	394	31	14	17
Odiorne and Simmons (1904)	55	7	3	4
Cunningham (1921)	67	0	0	0
Southam and Linell (outside cases) (1923)	7	3	2	1
Lower (Higgins) (1928)	23	1	0	1
Rea (1931)	76	11	6	5
Taylor (1938)	50	15	8	7
Total	672	68	33	35
Percentage		10.1	48.5	51.5

and in the abdominal testicle. Accordingly, I have gathered together from the literature papers which present the number of malignant growths in the inguinal and in the abdominal testicle from the same hospital. In this series of 672 malignant testicular tumors there were 68 in undescended testicles (10.1 per cent); of these 33 were abdominal and 35 inguinal, that is, 48.5 to 51.5 per cent. Again the proportion is the same. The difference between 48.5 ± 6.0 per cent and 14.3 ±

0.7 per cent is 34.2 ± 6.1 per cent, a figure which is more than five times its standard error and therefore statistically very significant.

It will be of interest to carry out the same calculations that Bulkley attempted. Of the 500,000 male patients admitted, 14 had malignant growth in the abdominal testicle, that is, 1 in about 36,000. Five of the nine papers gave the incidence of undescended testis as 930 in about 240,000 patients admitted, or 1 to 256. One may estimate that the percentage of abdominal testicles was 14.3 (table 3). This would make 133 abdominal retentions in 240,000 male patients admitted, or about 1 in 1,800. By dividing 36,000 by 1,800 one gets a quotient of 20, indicating that 1 abdominal testicle out of 20 undergoes malignant change.

Making the same calculations regarding the inguinal testicle, one finds that 1 male patient in 30,000 has malignant growth of the inguinal testicle; and that 1 male patient in 365 has inguinal testicle. By dividing

TABLE 6.—*Incidence of Nondescent of Testis in Hospital Admissions*

Author	Location	Admissions of Male Patients	Admissions for Undescended Testis
MacKenzie and Ratner	Montreal	50,000	105
Hinman and Benteen	San Francisco	39,359	155
Owen and Christoffersen	Illinois	28,000	15
Southam and Linell	Manchester	57,000	413
Young	Baltimore	12,500	60
Campbell	Boston	50,000	182
Total		236,859	930
Ratio			1:256

30,000 by 365 one gets a quotient of 82, indicating that 1 inguinal testicle of about 80 undergoes malignant change. The difference is between about 1 per cent and about 5 per cent. Taken together, there are 2 malignant growths to about 100 undescended testicles, a ratio which is of the same order of magnitude as the (1:64) shown in table 3.

COMMENT

While most writers have recognized that the undescended testicle is more prone to undergo malignant change, they disagree widely as to whether the inguinal or the abdominal testicle is the more liable to undergo such a change. The majority have inclined to the belief that the abdominal testicle is less liable to be affected by the malignant tendency, and this is reflected in the practice of putting the inguinal testicle back into the abdomen if it cannot be brought down into the scrotum. It has been thought that the inguinal testicle was more exposed to trauma.

A study of the tables and their accompanying notes will indicate that the incidence of nondescent in the general adult male population is

0.23 ± 0.0015 per cent and that the incidence of nondescent in cases of malignant growth in the testis is 11.0 ± 0.3 per cent. The difference is 10.77 ± 0.33 per cent, a figure which is thirty-two times its standard error. Of over 2,000 undescended testicles, the abdominal constitute 14.3 ± 0.7 per cent of the total, and of 840 undescended testicles involved in malignant growth the abdominal constitute 41.3 ± 1.7 per cent. The difference is 27 ± 1.8 per cent, a figure which is fifteen times its standard error. Hence one may say that data now available are sufficient to enable one to conclude unequivocally that the undescended testicle is more liable than the scrotal to malignant change and that the abdominal testicle is more liable to malignant change than the inguinal.

On the basis of accumulated statistical data, it is suggested that the practice of placing the inguinal testicle within the abdomen should be abandoned altogether. The abdominal testicle should always be explored and brought to the scrotum if possible, or at least into the inguinal canal. If neither of these improvements can be accomplished, the testicle should be excised. Malignant change in the abdominal testicle proceeds to the inoperable stage before the patient is aware of any enlargement.

Some may argue that it is not wise to operate on 20 abdominal testicles to prevent cancer in 1. Were it not that there are associated conditions which often indicate operation, I should be inclined to agree. However, hernia is frequently associated,[2] and during the operation for this, the testis should be brought into a region where it is palpable or excised. There are often psychologic reasons also why it is best to try to place the testis in the scrotum.

To carry this program into effect in a case of bilateral abdominal testicle is admittedly most difficult. There is convincing evidence that the man with bilateral maldescent is in much greater danger from cancer than the man with but one nondescended testicle. All are agreed that nondescent and cancer are more common in the right testicle. While there are no figures to support the hypothesis, it seems likely that of two abdominal testicles the left would ordinarily be nearer the internal ring and therefore more capable of being brought into the canal. If the other testicle cannot be brought into the canal, it should be excised. Of course, no surgeon would recommend bilateral excision to prevent cancer, but it seems that the testes should (and in most instances can) be brought at least into the inguinal canals. Thereafter, the patient with undescended testicle, whether the subject of orchiopexy or not, should be observed by his physician at frequent intervals. There is no evidence, as yet, that

2. Of the 34 abdominal testicles observed at the Peter Bent Brigham Hospital, 14 were associated with hernia on the same side and 3 with hernia of the opposite side, the opposite testicle being normally descended.

orchiopexy prevents cancer; further data must accrue. The proved overwhelming susceptibility of the undescended testicle to malignant change should make such a testicle the object of unrelenting suspicion.

SUMMARY

Six reasons why confusion has existed in the literature on undescended testicle are: (1) lack of knowledge of the statistical method on the part of physicians; (2) the serious misquotation of one author by another; (3) failure to use a uniform nomenclature; (4) the tendency to depend on isolated or selected series; (5) the continuing influence of papers written in an earlier period, when the abdomen was infrequently explored; (6) the neglect to indicate in which cases the condition was bilateral because patients rather than testes are enumerated.

The earlier literature has been investigated and the original contributions have been consulted in each case. Many of the earlier ideas about malignant change in the undescended testicle resulted from the failure of authors to consult original sources.

From the literature since 1900 there have been collected: (1) a group of about 500,000 cases in which male patients were admitted to hospitals; (2) a series of 1,413 cases of undescended testicle in which the incidence of malignant change is known; (3) a series of 2,119 cases of undescended testicle in which the relative incidence of abdominal and inguinal nondescent is known; (4) a series of 672 cases of malignant growth in the testis in which the relative frequency of abdominal and inguinal nondescent is known.

Table 7 lists all cases of nondescent at the Peter Bent Brigham Hospital for a period of twenty-seven years.

TABLE 7.—*Undescended Testicles at the Peter Bent Brigham Hospital from 1913 to 1939 in About 50,000 Male Patients*

Type of Undescended Testis	Testicles Showing No Malignant Change			Testicles Showing Malignant Growth			Total
	Right	Left	Total	Right	Left	Total	
Abdominal	17	16	33	1	..	1	34
Inguinal	43	42	85	..	1	1	86
Superficial inguinal	26	20	46	..	..	..	46
Inguinal + superficial inguinal	69	62	131				132
Pubic	7	5	12	..	..	..	12
High scrotal	2	1	3	..	..	..	3
Perineal	0	1	1	..	..	..	1
Total	95	85	180	1	1	2	182*

* This represents 158 patients; 24 had bilateral nondescent of testicle. Of the 2 patients with malignant growth in the undescended testicles, 1 had bilateral inguinal nondescent of testicle.

CONCLUSIONS

From the data presented the following conclusions may be drawn:

The incidence of malignant change in the testicle is statistically higher in undescended testicles than in normally descended testicles.

Inguinal nondescent is more frequent than abdominal nondescent. In series including children, the incidence of abdominal nondescent constitute about 10 per cent of the total incidence of nondescent; in series with few or no children, the incidence of abdominal nondescent constitutes about 20 per cent.

The incidence of malignant growth in the testicle is statistically higher in cases of abdominal nondescent than in cases of inguinal nondescent. One in about 20 abdominal testicles shows malignant change. One in about 80 inguinal testicles shows malignant change.

Combined hospital figures reveal about equal numbers of abdominal and inguinal malignant growths. This is because the proportion of inguinal to abdominal testicles is about 4 to 1 and the proportion of cancerous inguinal to cancerous abdominal testicles is about 1 to 4.

Dr. F. A. Simeone, Urologic Fellow the Peter Bent Brigham Hospital, suggested the necessity of a statistical study of the literature.

Dr. J. B. Hamilton of the Yale University School of Medicine furnished the tables and the bibliographic lists used in preparing the paper written by him and Dr. J. B. Gilbert.

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TREATMENT OF URETERAL SPASM

OBSERVATIONS WITH SPECIAL REFERENCE TO THE USE OF EXTRACT OF MAMMALIAN SKELETAL MUSCLE

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The necessity for preserving the normal peristaltic activity of the ureter and thereby maintaining an undisputed right of way for the passage of the urine from the kidneys to the bladder has been accepted as an incontrovertible fact.

In his splendid publications on the physiology of the ureter, Trottner [1] has pointed out that this structure can be conveniently separated into three divisions—upper, middle and lower thirds. This division is based on the results of his physiologic and pharmacologic studies. Progressive peristalsis may commence in any of these divisions; eventually, the peristaltic activity will spread throughout the remainder of the ureter. If the ureter is unable to convey its contents to the bladder and this adynamic status prevails relatively long, then renal damage is an inevitable consequence. Such incidental accessory factors as gravity, descent of the diaphragm and transmitted renal filtration pressure are capable of aiding in the passage of urine through the ureter only in the presence of normal peristaltic activity in that organ. It is evident that normal ureteral peristalsis is as indispensable to the preservation of function of the renal parenchyma and calyceal system as the maintenance of the ureteral path free of mechanical obstruction.

INSULIN-FREE PANCREATIC EXTRACT

In 1926, Frey and Kraut [2] published a report of the isolation of a substance from urine which produced vasodilatation. It was suggested

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that this substance was secreted by and conserved in the pancreas, excreted in an inactive state into the circulation and finally excreted in an activated state by the kidneys. The depressor effect of this substance was attributed by Wolffe [3] to its property of neutralizing the pressor effect of epinephrine by moderating the sensitivity of the sympathetic nervous system. This was based on the premise that angiospasm was the effect of an imbalance of the sympathetic and parasympathetic nervous systems with ultimate predominance of the former.

Ten years later, Joseph Lazarus [4] reported the successful use of an insulin-free extract of pancreatic tissue in the treatment of occlusion of the ureter due to calculi and spastic conditions. The hypothesis on which this clinical experiment was founded was that excessive stimulation of the extrinsic and the intrinsic sympathetic nerve fibers occurred in the ureteral segment in which a calculus was lodged. Spasticity of the ureteral musculature in the contiguous wall followed this chain of events. Reviewing the satisfactory clinical results obtained by Wolffe, Findley and Dessen, who treated angina pectoris and spastic colitis with this depressor pancreatic extract, Lazarus was impressed with the possibilities of applying the same substance to sympathetic hyperactivity in the ureter in the presence of foreign bodies and various inflammatory changes. His results were encouraging, and in 1940 he reported uniformly good effects from the use of pancreatic tissue extract in more than 100 cases of ureteral occlusion due to calculi, spasm and stricture.

Carroll and Zingale [5] also published an account of their results in the treatment of renal colic with insulin-free extract of pancreatic tissue. They attributed the pain in renal colic (not always due to distention of the proximal ureteral segment) to ischemia of the nerve endings present at the site of ureteral muscle spasm. They contended that pancreatic extract relieves this ischemic state by producing relaxation of the affected portion of the ureter, thus permitting the affected part to return to its normal physiologic status.

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3. Wolffe, J. B.; Findlay, D., and Dessen, E.: Treatment of Angina Pectoris with Tissue Vasodilator Extract: Preliminary Report, Ann. Int. Med. **5**:625-642, 1931.

4. Lazarus, J. A.: Use of Insulin-Free Pancreatic Tissue Extract as Aid in Cystoscopic Treatment of Impacted Ureteral Calculi and Spastic Occlusions of Ureter: Preliminary Report, Urol. & Cutan. Rev. **40**:847-850, 1936; Further Observations on the Use of Insulin-Free Pancreatic Tissue Extract as Aid in Cystoscopic Treatment of Impacted Ureteral Calculi and Spastic Occlusions of Ureter, J. Urol. **43**:102-107, 1940.

5. Carroll, G., and Zingale, F. G.: A Clinical and Experimental Study of the Effect of Pancreatic Tissue Extract on the Ureters, South. M. J. **31**:233-236, 1938.

EXTRACT OF MAMMALIAN SKELETAL MUSCLE

In 1930, Ludwig Haberlandt,[6] while engaged in working out a research problem on frogs, noted the efficiency of Ringer's solution in eliciting an accelerated ventricular rate in the isolated ventricle in which the resected sinus had been left to beat. He demonstrated the presence of an active substance which he termed "cardiac hormone." This substance was proved to have the property of making a frog's heart beat again after it had remained in a dormant condition for two or three days. Numerous clinical applications of this substance were then attempted. Julius Bauer of Vienna reported some favorable results in treating angiospastic conditions with the so-called heart hormone. Clinicians throughout Europe became interested in the implications of Haberlandt's work. Gley and Kisthinios,[7] M. Schwartzman,[8] Fahrenkamp,[9] Korach,[10] Y. S. Shwartzman,[11] Nielsen,[12] Giroux,[13] Dimitracoff [14] and numerous others began to use various tissue extracts in the treatment of cardiovascular diseases, particularly hypertension, angina pectoris, endarteritis and angiospastic states.

According to the same reasoning by which Lazarus applied insulin-free pancreatic extract in the treatment of ureteral obstruction and spasm, it was felt worthy of the effort to study an extract of mammalian skeletal musculature in order to learn whether this extract possessed further pharmacologic properties analogous to the pancreatic extract, especially as related to the treatment of obstructive anomalies of the ureter.

Description.—In this study, we employed an extract of mammalian skeletal muscle which consists mainly of nucleosides derived from nucleic

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6. Haberlandt, L.: Cardiac Hormone, Wien. med. Wchnschr. **81**:527 and 566, 1931; Cardiac Hormone, Endokrinologie **6**:335-345, 1930.

7. Gley, P., and Kisthinios, N.: Existence of Blood Pressure Reducing Pancreatic Hormone, Wien. klin. Wchnschr. **43**:1530-1536, 1930.

8. Schwartzman, M. S.: Muscle Extract Treatment of Grave Vascular Diseases, Brit. M. J. **1**:492-493, 1931.

9. Fahrenkamp, K.: Cardiokinetic Muscle Extract in Treatment of Angina Pectoris, Aerztl. Rundschau **41**:7-9, 1931.

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12. Nielsen, O. J.: Therapeutic Application of Lacarnol (Cardiokinetic Muscle Extract), Ugesk. f. læger **93**:240-243, 1931.

13. Giroux, R., and Kisthinios, N.: Insulin-Free Pancreatic Extract in Raynaud's Disease, Bull. méd., Paris **45**:140, 1931.

14. Dimitracoff, C.: Insulin-Free Extract of Pancreas in Obliterating Arteritis, Crón. méd. mex. **29**:559-566, 1930.

acid. This solution is biologically standardized so that its content has a uniform amount of active nucleosides. It does not contain any choline, histamine, epinephrine or related substances; it is free of pharmacologically significant amounts of potassium or calcium ions. This extract has been found effective in the treatment of angina pectoris and various other angiospastic conditions. Experimental evidence indicates that tissue extracts derived from mammalian skeletal muscles dilate the coronary vessels of mammalian hearts, thereby increasing the rate of flow through them. Ludwig [15] has reported a slight acceleration of the pulse with no change in the electrocardiogram when this muscle extract is given intravenously to healthy persons. Buchholz [16] reported that even large doses had practically no effect on normal hearts; he noted slight redness of the face and subjective sensation of warmth. In collaboration with Czike, Buchholz observed the action on the respiratory apparatus and reported that inspiration and expiration became easier and that the residual air was diminished. We have not been able to find any reports of undesirable toxic reactions or cumulative effects following the use of this extract.

Dosage.—The selected extract was given hypodermically and intramuscularly in doses of 1.0 and 2 cc. In several cases the drug was given in repeated doses (i. e., every four hours for four doses). The preparation for oral administration was not used in this experiment.

Clinical Applications.—In the period from January 1941 to May 1941, during which this study was conducted, 17,000 patients were admitted to the Charity Hospital. Of this number there were admitted to the urologic service 315 white males, 80 white females, 390 Negro males and 94 Negro females. No notable differences were observed in the response of white and Negro or male and female patients.

The muscle extract was administered for the relief of pain to patients with a wide variety of urologic complaints. These included: acute pyelonephritis (9 cases); chronic pyelonephritis (32 cases); ureteral colic due to calculi (27 cases); ureteral colic with which no calculus could be demonstrated by roentgen examination (5 cases), and postcystoscopic reactions (3 cases). Slight or no relief was noted from the treatment of acute pyelonephritis (3 cases), chronic pyelonephritis (6 cases), ureteral colic due to calculi (8 cases), ureteral colic with which the presence of calculi could not be demonstrated by roentgen examination (3 cases) and ureteral spasm (5 cases).

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15. Ludwig, W.: Clinical Investigation of the Effects of Cardiac Skeletal Muscle Extract on Diseases of the Circulatory System, Klin. Wchnschr. **80**:1531, 1931.

16. Buchholz, B.: On the Clinical Experience with the Cardiac Hormone, Lacarnol, Deutsche med. Wchnschr. **57**:188-190, 1931.

Therefore, in a total of 91 cases of diverse urologic conditions, the muscle extract was administered for the alleviation of pain. In 66 cases (72.5 per cent) appreciable to complete relief was obtained, and in 25 cases (27.5 per cent) there was failure to obtain any desirable degree of relief.

No sedation was employed until it was obvious that the muscle extract was of no value in the case.

The average time for the relief of pain was six and one-half minutes. In this connection, we have noted that no desirable effects from the muscle extract can be anticipated if relief is not obtained within ten minutes.

Several interesting points were brought out in connection with this series. One patient who had attacks of angina pectoris associated with acute exacerbations of chronic pyelonephritis obtained relief for both

TABLE 1.—*Results of the Administration of Extract of Mammalian Skeletal Muscle for the Relief of Pain*

Conditions Treated for the Relief of Pain	Appreciable to Complete Relief (Cases)	Slight to No Relief (Cases)	Total Cases
Acute pyelonephritis	6	3	9
Chronic pyelonephritis	26	6	32
Ureteral colic due to calculi (presence of calculi proved by roentgen examination)	19	8	27
Ureteral colic (presence of calculi not proved by roentgen examination)	2	3	5
Ureteral spasm	10	5	15
Postcystoscopic reaction	3	0	3
Total	66	25	91

conditions every time that she received an injection of the skeletal muscle extract. Another patient who suffered severe attacks of renal colic and persistent epigastric pain (peptic ulcer demonstrated in gastrointestinal series) was completely relieved of discomfort after injections on four separate occasions.

Two errors in diagnosis also are included in this series. One patient who had suffered from pain believed due to a possible chronic pyelonephritis failed to obtain any relief following two injections of the extract. Further study revealed that the pain was due to an ovarian cyst; when this was excised, the pain disappeared. Another patient who gave a history suggestive of renal colic failed to obtain any relief from injections of the extract. She later proved to have colitis. Two patients with renal colic (proved by roentgen examination to be due to calculi) passed calculi within thirty minutes after the injection of the muscle extract.

Eighty-two cystoscopic examinations were performed; after this procedure, 1 to 2 cc. of muscle extract was routinely given hypodermically.

The following conditions were included in this series: acute pyelonephritis (3 cases), chronic pyelonephritis (28 cases), hydronephrosis (3 cases), infected hydronephrosis and pyonephrosis (4 cases), nephroptosis (2 cases), perinephric abscess (2 cases), ureteral colic due to calculi (19 cases), ureteral colic in which no calculi were demonstrated by roentgen examination (3 cases), abnormal insertion of the ureter (4 cases), ureteral spasm (9 cases), ureteral kink with hydronephrosis (1 case), ureteral stricture (13 cases), carcinoma of bladder (2 cases),

TABLE 2.—*Reaction and Nonreaction After Cystoscopic Examination with Routine Administration of Muscle Extract After This Procedure in Eighty-Two Cases*

Condition	Cystoscopic Examinations After Which There Was		Total Examinations
	No Postcystoscopic Reaction	Postcystoscopic Reaction	
Acute pyelonephritis	3	0	3
Chronic pyelonephritis	28	0	28
Hydronephrosis	3	0	3
Infected hydronephrosis and pyonephrosis	4	0	4
Nephroptosis	2	0	2
Perinephric abscess	2	0	2
Ureteral colic due to calculi (presence of calculi proved by roentgen examination)	17	2	19
Ureteral colic (presence of calculi not proved by roentgen examination)	2	1	3
Abnormal insertion of ureter	3	1	4
Ureteral spasm	8	1	9
Ureteral kink with hydronephrosis	1	0	1
Ureteral stricture	12	1	13
Carcinoma of the bladder	2	0	2
Carcinoma of the cervix vesicae with extension into the bladder	5	1	6
Chronic cystitis	14	1	15
Hodgkin's disease	1	0	1
Tuberculous nephritis	2	0	2
Hypernephroma	1	0	1
Total	110	8	118

carcinoma of the cervix vesicae with extension into the bladder (6 cases), chronic cystitis (15 cases), Hodgkin's disease (1 case), tuberculous nephritis (2 cases) and hypernephroma (1 case).

Postcystoscopic reactions occurred in 1 case of each of the following urologic conditions: ureteral colic in which no calculus was demonstrated by roentgen examination, abnormal insertion of the ureter, ureteral spasm, ureteral stricture, carcinoma of the cervix vesicae with extension into the bladder, and chronic cystitis. Postcystoscopic reactions also occurred in 2 cases of ureteral colic due to calculi.

Therefore, in a series of 82 cases in which cystoscopic examinations were made and in which muscle extract was administered routinely after the procedure was completed, there were 8 (9.8 per cent) instances

of postcystoscopic reactions and 74 (90.2 per cent) cases in which no postcystoscopic reactions occurred.

In this series, there were 6 cases in which one or both ureters could not be catheterized because of marked spasm. From 1 to 2 cc. of the muscle extract was then given to the patients intramuscularly; after this injection (average time six and one-half minutes) it was possible to introduce catheters up the ureters with relative ease. In 1 patient in this series who had had several pelvic lavages at intervals of six weeks marked cystoscopic reactions always developed. Before the last three cystoscopic treatments, she received 1 cc. of muscle extract hypodermically and she suffered no postcystoscopic reactions.

Controls.—Mammalian skeletal muscle extract in 1 cc. doses was injected hypodermically into 20 patients with electrocardiographic evidence of myocardial disease for the purpose of studying the effect on blood pressure. The findings may be summarized as follows:

1. No appreciable lowering of blood pressure occurred in patients with normal blood pressure.

2. Notable drop in blood pressure occurred only in cases of hypertension; the systolic pressure underwent a greater decrease than the diastolic pressure. This drop in blood pressure was governed by two factors:

(*a*) The younger patient sustained a greater drop in blood pressure for a longer period than the older patient with the same basal blood pressure.

(*b*) The greater the degree of hypertension, all other factors being equal (e. g., age, cardiac status), the greater the drop in blood pressure after the administration of the drug.

3. The lowered blood pressure that occurred after the injection of muscle extract persisted from forty minutes to sixteen hours.

4. In no case was the induced lowering of blood pressure followed by any subjective complaints (e. g., vertigo, headache), loss of consciousness or cardiac decompensation.

We believe that the explanation for the blood pressure findings just summarized rests on the premise that the mammalian muscle extract used in this study tends to bring about a relaxation of the smooth musculature in the entire body. This hypothesis enables us to explain why the degree of lowering of the blood pressure and sustenance of the reduced level is greater in younger patients, in whom sclerotic changes in the vascular walls tend to be less pronounced, than in the older patients.

It should be noted that reduction of the blood pressure with extract of mammalian muscle has not been a universally consistent finding. An editorial in *Lancet* commented on the use of tissue extracts as follows: "As regards hypertension, opinions are diverse. Some record definite

lowering of pressure with considerable clinical improvement; others using the same preparations have seen little or no effect."

Finally, skeletal muscle extract (1 cc. hypodermically) was given to children, patients with cardiac decompensation, patients with demonstrable hepatic and renal disease and patients subject to attacks of bronchial asthma (not during attacks). In no instance were we able to demonstrate any undesirable side reactions, either immediate or delayed.

SUMMARY

Some of the experimental and clinical observations with insulin-free pancreatic extract and extract of mammalian muscle are reviewed.

An extract of skeletal mammalian muscle was used for the purpose of relieving pain, preventing and treating postcystoscopic reactions in cases of diverse urologic conditions and relieving various obstructive anomalies of the urinary tract with encouraging results.

No undesirable clinical effects or side reactions were encountered with this mode of treatment.

The extract of mammalian skeletal muscle used in this study was supplied by the Winthrop Chemical Co., Inc.

RECONSTRUCTION OF THE STOMACH OUTLET IN GASTRIC RESECTION

A SIMPLE SUTURE FOR USE WITH THE BILLROTH 2 ORALIS TOTALIS TYPE OF OPERATION

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The most popular procedure for anastomosing the stomach with the jejunum in the Billroth 2 type of gastric resection is the end to side anastomosis (terminolateral gastrojejunostomy), i. e., the Billroth 2 oralis totalis type. The operation has one disadvantage; the wide stomach outlet, consisting of the entire transverse section of the stomach, permits rapid emptying of the stomach and consequently considerable shortening of the second or gastric phase of digestion. Several methods have been suggested for narrowing the width of the anastomosis. Usually, the proximal half of the divided stomach is closed while the distal part is left open to be anastomosed with the jejunum (Billroth 2 oralis inferior), or the distal part is closed and the proximal half anastomosed (Billroth 2 oralis superior). This method leaves one weak point, and that is the meeting of the closed part and the anastomosis—the three corner point. Billroth aptly called this point *Jammerecke* (Wailing Wall). Lahey [1] protects this point by suturing the jejunal loop on the closed part of the stomach outlet. To eliminate this weak point, to simplify the procedure of narrowing the gastric transverse section and particularly to reconstruct the shape of the stomach to the most natural possible anatomic conditions, I recommend a simple procedure. No originality is claimed. Haberer [2] used a similar method in his modification of the Billroth 1 type of resection. With his device it is possible to narrow the transverse section of the stomach so far that it can be anastomosed end to end with the duodenum. I performed his operation twice and found it satisfactory. It was not difficult to transfer Haberer's modification to the Billroth 2 type of resection. However, I simplified the technic and thus changed it in some respects.

The operation is performed as follows: The stomach and the duodenum are exposed in the usual way. The vessels of the part to

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From the Lankenau Hospital, service of Dr. George P. Müller.

1. Lahey, F. H., and Marshall, S. F.: Technique of Subtotal Gastrectomy for Ulcer, Surg., Gynec. & Obst. **69**:498, 1939.

2. Haberer, H.: Gegenwärtiger Stand der operativen Behandlung des Magen- und Zwölffingerdarmgeschwüres, Deutsche Ztschr. f. Chir. **200**:212, 1927.

be resected are ligated and separated. The stomach is separated between two soft clamps. Then follow the separation of the duodenum and the closure of the stump. The jejunum is brought in contact with the stomach in a retrocolic or an antecolic position, its afferent loop toward the lesser, its efferent loop toward the greater, curvature. Now the anastomosis between the transverse section of the stomach and the jejunum is made. In order to narrow the stomach outlet evenly throughout, a suture is recommended which will include more tissue on the gastric side than on the jejunal side, i. e., one that will produce a pleating in of the terminal stomach wall. The posterior stomach wall is shortened by a pleating-in serosa suture and the anterior wall by a pleating-in mucosa suture.

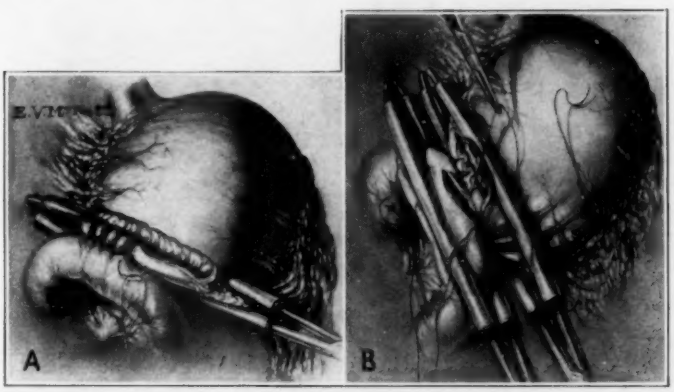

Fig. 1.—*A*, transverse section of the stomach to be anastomosed with the jejunum after the Billroth 2 oralis totalis type of gastric resection. The posterior serosa-muscularis suture is interrupted and led horizontally through the stomach wall and vertically through the jejunum, thus pleating in the posterior gastric wall. After two such sutures have been done, the stomach clamp is opened temporarily. *B*, the mucosa muscularis-serosa suture is continuous. To take the knot of this suture away from the corners of the anastomosis, i. e., to take away the weak points from the curvatures, the suture starts from the middle of the posterior wall. It closes first one half of the anastomosis, then the second half. Both sutures meet in the middle of the anterior wall. When either suture reaches the anterior wall, it becomes a pleating-in suture. In this drawing the half of the anastomosis toward the greater curvature is being closed. The "loop on the mucosa" type of suture is used. To shorten the gastric wall the loop on the gastric side is made wider than the loop on the jejunal side. Furthermore, the jejunal loops are placed close to each other. The pleating effect, if necessary, may be increased by leading the jejunal loop not horizontally but vertically through the jejunum.

The serosa suture between the posterior gastric wall and the jejunum commences at the lesser curvature and is interrupted. In order to include more tissue on the gastric side than on the jejunal side the

direction of the stitch is horizontal on the gastric and vertical on the jejunal side. The suture is led first through the serosa-muscle layer of the gastric wall parallel to the stomach outlet, i. e., horizontally, with a broad "bite" of tissue. It is then led through the jejunal serosa-muscularis right above the insertion of the mesentery in a vertical direction and locked (fig. 1 *A*). This causes a shortening of the stomach wall while the jejunum wall remains unaffected. After two such sutures have been done, the soft stomach clamp should be opened temporarily to allow the stomach wall to contract. After the serosa suture along the posterior gastric wall is completed, the jejunum is opened (with as small an opening as possible), and the mucosa-muscularis-serosa suture is carried out. It is a continuous catgut suture, simple along the posterior stomach wall but pleating in along the anterior wall. To take

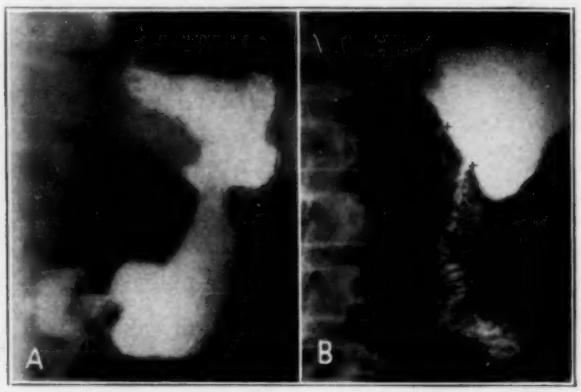

Fig. 2.—*A*, roentgenogram showing large penetrating ulcer in the proximal third of the lesser curvature, causing hourglass deformity of the stomach. Biopsy revealed a benign lesion. Note the deep crater in the lesser curvature and the approximate line of resection. *B*, roentgenogram taken nine months after resection of four fifths of the stomach. The operation performed was the antecolic Billroth 2 oralis totalis type of resection with pleating in of the stomach. Note the narrowed outlet (*x-x*) above the bottom of the stomach; this causes a valvelike action which prevents the dumping of food. The anastomosis drains well into the efferent jejunal loop.

the knot of this suture away from the corners of the anastomosis, i. e., to take away the weak points from the curvatures, the suture starts from the middle of the posterior wall. It is first led toward the greater curvature, closing this half of the anastomosis. A second suture, also starting from the middle of the posterior wall, closes the other half and meets the first suture in the middle of the anterior wall. When either suture reaches the anterior wall it becomes a pleating-in suture. It is led so that it shortens the anterior stomach wall but not the jejunal wall.

I use the "loop on the mucosa" type of suture. To shorten the gastric wall the loop on the gastric side is made wider than the loop on the jejunal side. Furthermore, the jejunal loops are placed close to each

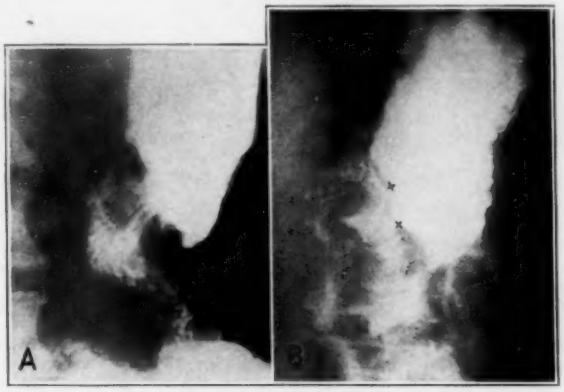

Fig. 3.—*A*, roentgenogram taken four months after resection of the stomach for stenosing pyloric ulcer. The type of resection was the retrocolic Billroth 2 oralis totalis with pleating in of the stomach. Note the restoration of the lift of the stomach achieved by drawing the greater curvature up to the lesser curvature. *B*, roentgenogram taken seven months after gastric resection for duodenal ulcer. The type of resection was the antecolic Billroth 2 oralis totalis with pleating in of the stomach. Valvelike action at the stomach outlet (*x*-*x*) was obtained, and the anastomosis drains well.

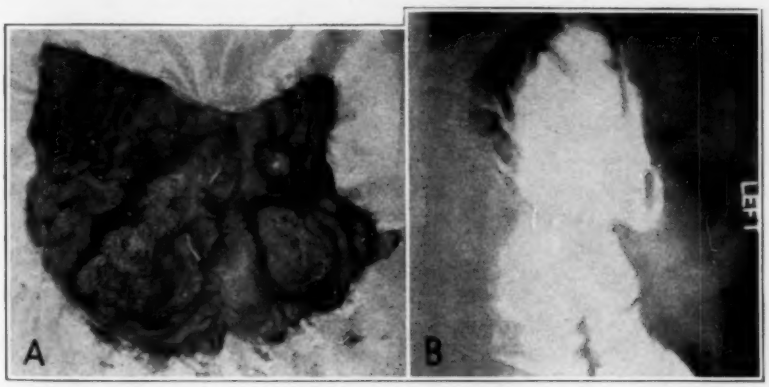

Fig. 4.—*A*, specimen of a gastric resection for Hodgkin's disease of the stomach. *B*, roentgenogram taken four months after resection of three fourths of the stomach. The type of resection was the retrocolic Billroth 2 oralis totalis with pleating in of the stomach.

other. Figure 1 *B* demonstrates this principle better than any description. If necessary, the pleating effect may be increased by leading the loop through the stomach horizontally and through the jejunum ver-

tically. After this suture is completed, the clamp is opened; either a simple interrupted or a continuous Lembert suture approximates the anterior gastric and the jejunal serosa.

This simple pleating-in suture narrows the stomach outlet more than half of its circumference; it attempts to reconstruct the stomach outlet so as to produce as normal anatomic conditions as possible. Owing to the difference in the length of the curvatures, the half toward the lesser curvature is shortened at the expense of the greater curvature, i. e., the greater curvature is drawn up toward the lesser curvature (figs. 2, 3 and 4). Thus the new outlet comes to lie above the axis of the stomach, as the pylorus does in a normal stomach, i. e., the lift of the stomach is restored and a dumping of the food avoided.

I have employed the pleating-in suture in 7 cases in which gastric resection was performed (2 cases of gastric ulcer; 1 of Hodgkin's disease of the stomach, 1 of pyloric ulcer, 1 of gastrojejunal ulcer and 2 of duodenal ulcer). In all cases the functional result was good, as demonstrated symtomatologically and roentgenologically.

SUMMARY

A simple suture for narrowing the stomach outlet in gastric resection of the Billroth 2 oralis totalis type is described. The principle of this suture consists of pleating in the stomach wall.

REVIEW OF UROLOGIC SURGERY

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KIDNEY

Resection of the Kidney.—Garcia and Galvez [1] point out that partial nephrectomy is indicated only in those cases in which the remaining portions of the kidney are in sufficiently good condition, both functionally and anatomically, to justify expectation of functional efficiency after this conservative operation. Such cases are relatively few since pathologic processes affecting the kidney usually involve the entire organ. Care must be taken also to ascertain that the blood supply is adequate and that the evacuation of the urine is normal; if these conditions are not fulfilled, operation should not be performed. If these conditions are fulfilled, then after removal of the cause of the lesions, perfect repair and cicatrization of the operative wound are possible, and function of the remaining portion of kidney will be all that can be desired.

Until recently, partial nephrectomy was considered appropriate only in cases of solitary cyst of the kidney, small localized benign tumor, in certain cases of renal trauma and cases of double kidney in which a painful syndrome or pathologic processes affect only one of the excretory

1. Garcia, A. E., and Galvez, I.: La nefrectomia parcial, Rev. argent. de urol. **10**:209-234 (March-April) 1941.

systems. Now, however, a new field of usefulness for the procedure has been found, namely, cases of renal lithiasis; in these, cuneiform resection of the kidney at a site corresponding to that of the one or more calices involved may be the operation of choice, since the difficult procedure of extracting fragments of impacted stone is thus avoided.

The technic, which is relatively simple, must face two fundamental problems, namely: (1) The operation must assure the circulation of blood in the organ together with complete hemostasis of the sectioned surface of the parenchyma, and (2) the operation must repair the excretory tract, if this has been compromised by the portion resected, with care not to interfere with emptying. If possible, the larger vessels corresponding to the zone to be resected must be ligated in advance of resection. The sectioned surface must bleed profusely as evidence of the good circulatory condition of the remaining parenchyma except in cases in which the vascular territory is exactly delineated and in which hemorrhage is less profuse.

After the site of section has been chosen, the sectioned surface is made in the shape of a wedge; two flaps are cut in the remaining parenchyma to facilitate, by coaptation, hemostasis and cicatrization. Meticulous hemostasis is basic to the technic. Separate ligature is impossible for arteries of small caliber, and it is necessary to place U-shaped catgut sutures which serve the twofold purpose of stopping bleeding and approximating the edges of the wound. These sutures should be reenforced with perirenal fat (or with the capsule of the organ folded over itself to increase resistance) interposed between the edges of the wound. Other smaller sutures, single or U-shaped, are then placed along the margins.

The second problem, repair of the excretory tract provided it has been involved in the section, is accomplished by separate catgut sutures of the calices or the pelvis at the same time that separate ligation of vessels is carried out. Ligation by temporary compression of the pedicle to produce hemostasis is favored. If resection is performed at the upper pole of the kidney and if it is considered desirable to leave a pelvic drain, a sound may be placed through the open calix, the opening of the calix being reduced with partial suture. Care must be taken not to interfere with the emptying of the organ. This emptying is assured by repair of the pelvic wound, if one exists, freeing the ureter and the pelvis from possible adhesions and fixing the organ in the best position to facilitate the flow of the urine. This nephropexy is accomplished with the capsule; two flaps are cut from what remains of the capsule.

Possible complications are hemorrhage and urinary fistula. The former may be immediate or late; it usually occurs after eight to fifteen days. Late hemorrhage after nephrostomy is usually of grave portent, and, if persistent, secondary nephrectomy will be necessary. Urinary fistula is not likely to appear if there has been no interference with the

excretory apparatus. If a calix or the pelvis has been opened, careful suture will be the best means of avoiding fistula. If one does appear, every effort must be made to find and repair it.

Garcia and Galvez report a case of multiple caliceal lithiasis in a kidney with double pelves and ureters. Partial nephrectomy was indicated for the lower portion of the double organ. The case was complicated by the presence of an anomalous artery at the upper pole; the ligation of this artery apparently was the cause of the urinary fistula which appeared at this site on the eighth day after operation. The fistula discharged urine whenever the patient was recumbent but not when he was in a sitting position. The patient was maintained in the latter position, and the fistula closed on the fiftieth postoperative day. Formation of the fistula was attributed to development of a necrotic region at the point of ligation of the anomalous artery. Although every effort should be made to keep such a vessel intact, there are cases similar to this in which the vessel interferes with the operation. The risk attending ligation must therefore be faced in order to accomplish the purpose of the operation, which, in this case, was saving the upper half of the kidney. The risk, however, is not small, and in less fortunate cases it is possible for results of the operation to be jeopardized.

Yunck and Forsythe[2] report 19 clinical cases of caliceal resection for stone. In 16 cases, prompt healing and minimal resistant infection occurred, with no recurrence of stone. In the other 3 cases, severe postoperative bleeding was present, and this may have been a factor in producing the poor end results.

The end results of the operation were studied in 13 dogs. In 10, the calix was resected by means of a scalpel with no deaths. Healing was prompt and was complete at the end of fourteen days. Normal parenchyma, in which there was no evidence of ascending infection, was observed within 2 mm. of the operative scar. Although there was microscopic evidence of calcium and formation of bone in the scar was noted in 1 case, in all cases the pelvis was completely reepithelialized, and subepithelial plaques were absent.

In 3 animals, the calix was resected with high frequency cutting current. Two animals died four and five days after operation, respectively. The third animal had marked local sepsis and no evidence of healing.

From these experiments, it appears that resection of the calix with the scalpel is definitely superior to resection with the high frequency cutting current.

Resection of a calix containing stone is indicated because: (1) resistant infection usually is not a factor; (2) healing is prompt, with

2. Yunck, W. P., Jr., and Forsythe, W. E., Jr.: Calyceal Resection: Report of Clinical and Experimental Cases, J. Urol. **46**:396-412 (Sept.) 1941.

little danger of permanent urinary fistula; (3) there is little postoperative decrease in function of the kidney, as demonstrated by comparison of the preoperative and postoperative levels of urea and the determinations of phenolsulfonphthalein; (4) in most cases stone does not occur at the operative site or in other calices.

Campbell [3] emphasizes the importance of conserving renal tissue in surgical procedures on the kidneys. He states that resections when feasible are being performed more frequently than formerly. He reports the cases of 41 patients who underwent renal resection; there were 2 deaths—a mortality rate of 5 per cent.

Campbell tabulates the indications for resection as follows:

I. Normally formed kidney:

(*a*) Localized hydronephrosis due to obstruction of the calices and with or without infection or stone.

(*b*) Extension of large pelvic stone into a single calix.

(*c*) Solitary cyst or localized multilocular cystic disease.

(*d*) Benign neoplasm (rare).

(*e*) Certain cases of renal trauma with localized (polar) fragmentation or maceration and the reminder of the organ sound.

II. Anomalous kidney:

(*a*) Reduplicated pelvis with one sound pelvoparenchymal segment and the other diseased by hydronephrosis, infection or calculus associated with obstruction (chiefly stricture), infection or an ectopic opening of the corresponding ureter.

(*b*) Horseshoe kidney: 1. When the condition itself causes symptoms, chiefly pain, and in the absence of other disease.
2. When the conditions indicated under II *a* involve half of the horseshoe kidney or, as in 3 of our cases, involve a reduplicated pelvis on one side of a horseshoe kidney.

(*c*) Same as II *b* but for removal of the diseased renal segment in crossed ectopia, sigmoid, L, discoid or other forms of fusion anomaly.

III. In congenital or surgical solitary kidney with a resectable lesion. This includes the clinical equivalent in which the function of the opposite kidney is low (e. g. nephritis or congenital hypoplasia) but its removal is contraindicated.

Resection is not advisable in cases of carbuncle, tuberculosis or neoplasm. Because a large percentage of congenital anomalies are associated with ureteral obstruction and because the condition of the ureter will influence the choice of operation, a good ureterogram is as important as a good pyelogram. Often, the entire ureter draining the diseased renal segment is dilated to the ureterovesical opening, or it is ectopic. Under these circumstances, complete ureterectomy is indicated, and it is advisable to start with removal of the ureter. Whether this is

3. Campbell, M. F.: Resection of the Kidney, J. A. M. A. **117**:1223-1229 (Oct. 11) 1941.

carried out in one or two stages depends on the age and the condition of the patient.

When total ureterectomy is indicated, the following three courses are open:

1. One Stage Ureteroheminephrectomy: For adults in good condition, ureteroheminephrectomy in one stage may be performed. The ureter is first disjoined at its lowermost end through a Gibson or low pararectal incision; it is mobilized as high as possible retroperitoneally and then removed with its attached resected renal segment through the usual loin incision for nephrectomy.

2. Two Stage Ureteroheminephrectomy (Initial Renal Resection): When the condition of the adult patient is less certain, initial renal resection and partial ureterectomy may be performed with subsequent removal of the remaining ureter if the condition of the patient permits. Campbell considers this the best procedure for all children who require total ureterectomy, even for those in good physical condition.

3. Two Stage Ureteroheminephrectomy (Initial Mobilization of the Lower Part of the Ureter and Cutaneous Ureterostomy): When the condition of either the child or the adult patient is poor, and a two stage operation is definitely indicated from the outset, Campbell prefers to begin with an attack on the lower end of the ureter. At the first operation the ureter is disjoined from its point of origin, if ectopic, or from its junction with the bladder if the obstruction is in this region or if the ureter is widely dilated to its termination. The ligated cauterized proximal end is covered by a piece of dam fastened as a hood over the end of the ureter by a tightly tied ligature. The stump of the ureter is mobilized upward as far as possible, usually to the level of the posterior portion of the ilium. The mobilized lower end of the ureter is then brought out through a stab incision 2 or 3 cm. mesial to the level of the iliac crest and anchored to the cutaneous layer with two or three fine sutures. If the cut end of the ureter is turned back on itself in cuff formation for 1.5 or 2 cm. and kept moist for a few days by means of gauze soaked in physiologic solution of sodium chloride, necrosis is not likely to occur. In performing cutaneous ureterostomy in this manner it is good practice to fasten indwelling in the ureter a large four eye Robinson type catheter, which will facilitate healing of the wound by drainage of the infected urine to an appropriate receptacle. Later, when the condition of the patient permits, the kidney is exposed and the upper portion of the ureter is mobilized down to the point of cutaneous ureterostomy, which, by a racquet-shaped continuation of the loin kidney wound, is excised completely. The lower portion of the ureter and the stump left after ureterostomy are wrapped in a protective pad, and renal resection is carried out, the diseased tract being entirely removed.

Postoperative infection of wounds and renal necrosis caused by thrombosis and ischemia are the most frequent complications. Campbell has placed powdered sulfanilamide into contaminated wounds, using as much as 8 Gm. in the wounds of older children, with encouraging results.

Surgical Technic.—Digby [4] discusses an approach to the kidney by an incision over the twelfth rib. An incision is made directly over the twelfth rib; the rib is resected, and the periosteum above the subcostal vessels is incised. He claims that this gives much freer exposure to the kidney and avoids damage to the subcostal vessels and nerves and their branches. Injury to the pleura can be avoided by study of roentgenograms of the lower limit of the pleura before operation and by exposing the outer edge of the rib before incising it prior to resection. Digby carried out this incision in 13 cases without accident and states that this incision gave him free exposure in all cases.

Barnes and Bergman [5] discuss transperitoneal nephrectomy and report 17 cases in which this procedure was carried out.

To expose the kidney, the abdomen is opened by a longitudinal midrectus or pararectus incision; from this, a transverse incision is carried laterally over the mass of the tumor. The intestines are then displaced medially and retained by means of a large warm pack. The posterior peritoneal layer is incised laterally to the ascending or descending part of the colon. The ureter and the renal pedicle usually are readily identified; this facilitates their clamping and ligation under direct vision. In cases of malignant disease, the pedicle should be clamped as early as possible to prevent dissemination of tumor cells into the circulation. A greatly enlarged kidney may encroach on the inferior vena cava or the aorta to such an extent that it is difficult to separate the kidney from these large vessels. The inferior vena cava is easily injured, and its thin wall may be perforated while freeing adhesions between it and the enlarged kidney. When such an injury occurs while operating through a lumbar approach, it is difficult to control bleeding from the rent in the vena cava. The transperitoneal approach, however, gives adequate exposure so that an injury to the vena cava is easily seen and hemorrhage can be temporarily controlled by means of pressure. In Barnes and Bergman's series, injury to the vena cava occurred in 4 cases. In 2 of these, a clamp was applied and left in place; it was removed between the tenth and fourteenth postoperative days. In 2 other cases, the rent was sutured with fine catgut after clamping the vena cava. After removal of the mass, it is better to drain the

4. Digby, K. H.: The Twelfth Rib Incision as an Approach to the Kidney, Surg., Gynec. & Obst. **73**:84-85 (July) 1941.

5. Barnes, R. W., and Bergman, R. T.: Transperitoneal Nephrectomy, J. Urol. **46**:545-548 (Sept.) 1941.

retroperitoneal space through a stab wound in the lumbar region, although some surgeons prefer to close the renal fossa without drainage. The posterior and then the anterior layer of peritoneum are sutured with continuous catgut. The abdomen is closed without drains. A mattress suture is used to approximate the cut ends of the rectus muscle; the fascia is brought together with chromic forty day no. 1 catgut in a running suture, and the skin is approximated in the usual manner.

After removal of large renal neoplasms, the ultimate prognosis is poor. When operation results in a prolongation of normal life and activity for a year or more, Barnes and Bergman feel that the temporary relief given the patient by removing the large mass is worth the risk and the inconvenience of the operation.

Anomaly.—Woodruff [6] reports a case of triplication of the ureter and the renal pelvis. The patient, a man aged 74 years, was originally examined because of symptoms caused by an enlarged prostate. Cystoscopy revealed three normal-appearing renal orifices on the right side and one on the left. All three orifices were catheterized. A pyelogram revealed triplication of the renal pelvis.

Mallard [7] states that renal hypoplasia is essentially a diminutive normal kidney but that it is more subject to infection. The characteristic symptom of this type of kidney is pain. This pain is not due to the kidney being diminutive but is due to concurrent changes. There are no characteristic symptoms of hypoplastic kidney.

Renal hypoplasia of itself will not cause cardiovascular hypertension.

The diagnosis is made essentially by the characteristic pyelograms and the kidney shadow as seen roentgenographically. Usually, the upper calix is long; this particular calix and the pelvis of the kidney are in a straight line with the ureter.

The treatment for this type of kidney should be about the same as the treatment for a kidney of normal size. However, as a kidney of this sort has little function, nephrectomy is indicated more readily than for the normal kidneys under similar conditions.

Mallard reports 4 cases of congenital hypoplasia of the kidney. In 2, nephrectomy was performed because of infection.

Burt, Lane and Hamilton [8] report a case in which a triple kidney and three complete ureters were present on the right side; one ureter had an extravesical opening. There was a double kidney with a Y-shaped ureter on the left side. This is a rare anomaly, since a review

6. Woodruff, S. R.: Complete Unilateral Triplication of the Ureter and Renal Pelvis, J. Urol. **46**:376-379 (Sept.) 1941.

7. Mallard, R. S.: Congenital Renal Hypoplasia: Report of Cases, J. Urol. **46**:216-234 (Aug.) 1941.

8. Burt, J. C.; Lane, C. M., and Hamilton, J. L.: An Unusual Anomaly of the Upper Urinary Tract, J. Urol. **46**:235-240 (Aug.) 1941.

of the literature failed to disclose a report of any similar case. Lau and Henline reported a case of three complete ureters on the right side with three openings into the bladder. Their case was the only authentic one reported since their search of the literature revealed only 7 cases in which three or more ureters were present on one side; in each of these, however, evidence was insufficient to give complete proof of the existence of the ureters.

Fowler [9] states that 36 cases of bilateral renal ectopy have been reported in the literature. To these he adds 4 cases, making 40 to date. Of these, 22 were encountered clinically and 18 at necropsy.

These kidneys function normally and are not incompatible with health. Since the condition is not productive of symptoms, it frequently is unrecognized.

The lesions complicating bilateral ectopic kidneys are those commonly encountered in normally placed organs. The symptoms produced by complications are atypical, confusing and frequently misinterpreted. The preoperative diagnosis can be made only by routine urologic study, including intravenous and retrograde pyelography.

Treatment, when necessary, is similar to that employed for kidneys in normal position.

Stone.—Rupel and Brown [10] report a case in which nephrostomy with removal of the renal stone was carried out. Cystoscopic examination disclosed that only the left kidney was functioning. The right kidney was large, and the pelvis was filled with many stones. Nephrectomy was performed on the right side. Later, it was observed that the opposite kidney was obstructed by a stone lodged at the ureteral pelvic juncture. Nephrostomy was carried out; after this the patient's general condition improved. A panendoscope was inserted into the kidney through the nephrostomy opening. The renal pelvis was dilated with water, and the stone was seen, grasped and removed with the instrument. The patient showed a good operative result.

Ezickson and Morrison [11] discuss the role of the liver and the thyroid gland in the production of renal calculi. Studies were carried out to determine the incidence of hepatic dysfunction in an unselected group of patients who had had urinary lithiasis or had it at the time of the studies. They incorporated likewise studies pertaining to the basal metabolic rate and cholesterol determinations.

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9. Fowler, H. A.: Bilateral Renal Ectopia: A Report of Four Additional Cases, J. Urol. **45**:795-812 (June) 1941.

10. Rupel, E., and Brown, R.: Nephroscopy with Removal of Stone Following Nephrostomy for Obstructive Calculous Anuria, J. Urol. **46**:177-182 (Aug.) 1941.

11. Ezickson, W. J., and Morrison, L. M.: The Rôle of the Liver and Thyroid as Metabolic Factors in the Production of Renal Calculi, J. Urol. **46**:359-375 (Sept.) 1941.

Function of the liver was ascertained by estimation of the concentration of bile salts in the hepatic bile.

Twenty of the patients (34 per cent) revealed evidence of hepatic dysfunction. Of this group, 11 (61 per cent) had an abnormal basal metabolic rate, and 12 (50 per cent) had hypercholesteremia.

Of 17 patients with active urinary symptoms at the time the studies were made, 10 (59 per cent) had hepatic dysfunction. This was in contrast to the 42 patients without active urinary symptoms, 10 (24 per cent) of whom had hepatic dysfunction. These studies seem to reveal a definite relation between hepatic dysfunction, abnormal basal metabolic rate and hypercholesteremia.

Analysis of the results of these studies reveals that hepatic dysfunction is frequently associated with urolithiasis. The significance of this relation remains to be determined, but it seems that some disturbance in metabolism, in which both the liver and the thyroid gland play a part, is concerned with the development of certain types of urinary stones.

Lindahl and Bargen [12] state that renal calculi occur more frequently among patients suffering from chronic ulcerative colitis who undergo ileostomy in which the colon is not afterward removed than they do among patients suffering from chronic ulcerative colitis who do not undergo ileostomy. The basis for the formation of renal calculi might be the infected portion of the remaining part of the colon. Two of the many complications of chronic ulcerative colitis for which ileostomy has been performed without subsequent removal of the colon appear to be renal calculi and infection of the urinary tract. It does not seem likely that change in the metabolism of calcium and phosphorus occurs as the result of exclusion of the colon by ileostomy. The study of the authors seems to emphasize further the fact that ileostomy does not cure chronic ulcerative colitis and that complications continue to occur after performance of ileostomy that appear to be secondary to the infection still present in the remaining portion of the colon.

Boyd [13] states that recognition of the existence and the causes for the formation of renal calculus in cases of poliomyelitis is a matter of great importance. Most patients with poliomyelitis have had a sufficient loss of sensation to exclude or mask the symptoms ordinarily produced by renal or ureteral calculi. Time and again, cases of extensive formation of stone in the kidneys and even in the ureters occur with so little symptomatic evidence of the presence of the condition that no suspicion of the trouble exists until the disease is far advanced. Urinary infections are common in a large percentage of the cases of poliomyelitis in

12. Lindahl, W. W., and Bargen, J. A.: Nephrolithiasis Complicating Chronic Ulcerative Colitis After Ileostomy: A Report of Six Cases, J. Urol. **46**:183-192 (Aug.) 1941.

13. Boyd, M. L.: The Significance of Sensory Paralyses in Poliomyelitis Patients in Whom Renal Calculi Develop, J. Urol. **45**:647-651 (May) 1941.

which paralysis is sufficient to cause the patients to be bedridden for several months.

Urinary infection is usually blamed for the fever which appears when the stones begin to cause urinary obstruction, because there is so little pain; medicines are prescribed when roentgenograms and a complete urologic examination should be made.

Boyd reports the case of a boy who had the best medical attention and advice and yet when seen was in great trouble with severe chronic pyelonephritis on the left and a stone completely blocking the left ureter. The boy showed the effects of long-standing infection plus symptoms of high retention of nitrogen. Because of partial paralysis, the usual symptoms of obstruction from ureteral stone were absent. Recovery followed removal of the stone.

Boyd states that when infections of the urinary tract occur, they should be treated by urinary antiseptics and that some adequate measure should be employed for relief of the injurious effects which result from residual urine, whether intermittent catheterization or suprapubic cystotomy. A retention catheter almost always produces prostatitis, seminal vesiculitis and, eventually, epididymitis.

A suitable diet to maintain acidity of the urine is important. Citrus fruit juice should be given in moderation but not at all if the urine is alkaline or faintly acid. Alkaline drugs, such as milk of magnesia, sodium bicarbonate or saline laxatives containing alkalis, should not be given. An adequate intake of fluid should be maintained to prevent the urine from becoming concentrated. The patient's position should be changed frequently and as completely as possible, and he should lie on the abdomen an hour or two at a time every day as soon as the paralysis and general condition will permit.

Routine roentgenograms should be made at given intervals, and a complete urologic examination should be carried out if there is the least suspicion that the kidneys are infected or that a deposit of urinary salts in the urinary tract is taking place.

Calcium Plaques.—Vermooten [14] stated that the deposition of calcium in the renal papilla occurs among South African (Bantu) Negroes in a form indistinguishable from that occurring among Caucasians. The incidence, however, is much lower.

Although calcium plaques have been encountered among patients less than 20 and more than 80 years of age, there is a marked increase in incidence between the ages of 50 and 80 years; this indicates that age and its associated physiologic changes are important factors in causing this condition. The incidence is twice as great among men as it is among women.

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14. Vermooten, V.: The Incidence and Significance of the Deposition of Calcium Plaques in the Renal Papilla as Observed in the Caucasian and Negro (Bantu) Population in South Africa, J. Urol. **46**:193-200 (Aug.) 1941.

If patients who have cardiac disease and arteriosclerosis are excluded, calcium plaques are present among as many apparently healthy persons as among hospital patients. The precipitation of urinary salts on the calcium plaque must have a dietary or a metabolic controlling factor, for, although among South African Negroes the plaques form, renal calculi are not deposited on these plaques. The deposition of calcium in the renal papilla appears to be a change involving the collagen fibers in the renal papilla as a whole and is not limited to those fibers which surround the tubule.

Tuberculoma.—Bugbee [15] reports tuberculoma of the kidney of a woman 30 years of age. Cystoscopy revealed regions of congestion throughout the bladder. It was found that the left ureter was displaced laterally and that the vesical urine contained tubercle bacilli. A urogram of the left kidney disclosed a definite filling defect suggestive of a tumor of the renal pelvis. The kidney was removed and split throughout its length; the pelvis was found to be filled with a smooth pinkish mass which had the appearance of a renal tumor. Microscopic examination revealed that the original diagnosis of tuberculosis was correct.

In this case an early stage of the disease was represented in which the tuberculous process presents a definite tumor formation. Necrosis and formation of a cavity had not taken place. Although definite hemorrhagic regions were present in the bladder, the ureter apparently was not involved.

Polycystic Kidneys.—Norris and Herman [16] discuss theories of the origin of polycystic kidneys and describe 4 cases of congenital renal polycystic disease.

Evidence has been given that for a long period in fetal life development of the kidneys is normal. Focal cystic dilations of uriniferous tubules and collecting ducts occurring after differentiation of the metanephrogenic anlage and after the union of the elements with collecting ducts are followed by isolation as cysts of segments of these nephrons. Anastomosis among these cysts results from continued proliferation of these elements and from rupture of their walls. These changes are thought to be degenerative, since they resemble the stages in the normal degeneration of the mesonephros and of normally vestigial elements of the metanephros. In polycystic kidneys, therefore, the metanephros is abnormally provisional to a variable degree. Such an explanation appears to be applicable to most of the congenital anomalies associated with polycystic kidneys and to be compatible with the hereditary nature

15. Bugbee, H. G.: Tuberculoma of the Kidney: Report of a Case, J. Urol. **46**:355-358 (Sept.) 1941.

16. Norris, R. F., and Herman, L.: The Pathogenesis of Polycystic Kidneys: Reconstruction of Cystic Elements in Four Cases, J. Urol. **46**:147-176 (Aug.) 1941.

of the disease. The fundamental cause of polycystic disease of the kidneys must be in the germ plasm.

Lipoma.—Robertson and Hand [17] report 2 cases of primary intrarenal lipoma and discuss 12 cases reported in the literature in which the lipoma was removed surgically. Tumors of this type, because of their cortical and subcortical positions in the kidney, may attain considerable size before giving rise to symptoms. Pain and hematuria may call attention to the presence of such a tumor at an early date. Clinically, primary renal lipoma may be indistinct from primary renal carcinoma. Intrarenal lipoma may contain variable amounts of connective tissue, smooth muscle, myxomatous vascular tissue and cartilage, or it may reveal sarcomatous transformation.

A new concept of the origin of primary intrarenal lipoma is suggested, namely, that it arises from the embryonic connective tissue surrounding the developing collecting tubules. The embryonic connective tissues may be pushed to a cortical or a subcapsular position by the developing buds of the collecting tubules.

Rupture.—Williams [18] reports a case of subcapsular rupture of the kidney. The patient was a woman aged 31 years who had been injured in an automobile accident. Shortly after the accident hematuria occurred. On examination, abrasions were found over the right lower ribs and the right iliac crest. The right loin was tender and swollen, and the lower pole of the right kidney was enlarged. On the fifth day after injury, roentgenograms revealed an increase in the right renal outline. An excretory urogram did not disclose any abnormalities on the left side; on the right, the excretory return of the upper calices was normal, but the lower calices could not be defined. A vague opacity was noted in the region of the lower pole of the right kidney. A right retrograde pyelogram was then made, and the contrast medium was seen to pass out from two ruptured calices at the lower pole to collect in a puddle below the kidney. Williams expresses the opinion that a subcapsular rupture of two calices was present with the contrast medium freely entering the space caused by the stripping of the true renal capsule by blood and urine.

Perirenal Abscess.—Kindall [19] reports a case of perirenal abscess with the formation of gas and multiple metastatic abscesses of the lung caused by Friedländer's bacillus (Klebsiella pneumoniae). The patient was a man aged 63 years. This case is unique in that no similar one

17. Robertson, T. D., and Hand, J. R.: Primary Intrarenal Lipoma of Surgical Significance, J. Urol. **46**:458-474 (Sept.) 1941.

18. Williams, E. R.: Subcapsular Rupture of the Kidney: Case Report, Brit. J. Radiol. **14**:248-249 (July) 1941.

19. Kindall, L.: Perirenal Abscess with Gas Formation and Metastatic Pulmonary Abscesses Due to Friedlaender's Bacillus: A Case Report, J. Urol. **46**: 555-561 (Sept.) 1941.

has been found in the literature. Incision and drainage of the perirenal abscess were followed by satisfactory recovery. The source of the bacillus in this case was not known. The pyelograms were normal, and repeated cultures of the urine failed to yield the causative organism.

In a review of the literature, Kindall found that Friedländer's bacillus is present in almost every organ of the body, most frequently in the gastrointestinal tract and next frequently in the genitourinary tract; involvement of the lungs is rare.

Moore [20] has studied 50 cases of juxtarenal infection. Anatomically, he classifies 47 as perinephric and 3 as paranephric. Inflammation of the perinephrium may result from hematogenic infection or from direct spread from renal disease. These primary and secondary types differ fundamentally. In the primary type, the manifestations of the perinephric infection form the whole clinical and pathologic picture. Symptoms, signs or residual evidences of renal disease are not evident. Moore's observations lead him to agree with Vermooten that the common mechanism in cases of so-called primary perinephric abscess is infection from the blood stream, although he does not deny that in rare cases the perinephric tissue is infected from gross renal suppuration, such as carbuncle. In a great majority of cases, the bacteremia responsible for infection of the perinephric fat results from sepsis of the skin. Occasionally it is derived from infected abrasions, wounds or respiratory disease. Of the 50 cases studied, 37 were cases of primary perinephric infection. A history of previous boils or carbuncles was elicited in 10 cases. In 6 cases, some other infective lesion had been present, such as mastoiditis, coryza, infected sacral dermoid or influenza. The shortest interval noticed in these cases was four weeks and the longest one year. In 2 cases, trauma was known to be responsible for localization of the infection in the perinephrium. Staphylococcus aureus was the infecting organism in 73 per cent of the cases in which cultures were made. In 3 cases, Staphylococcus albus was responsible, and in 2, hemolytic streptococcus also was found. It may therefore be concluded that in most cases the predisposing lesion had been a staphylococcic infection of the skin. It is well to remember that suppuration by no means occurs in all cases. In some the perinephrium becomes thickened and inflamed without the formation of pus. The kidney is usually entirely normal. In rare cases, the abscess may spread across the midline and affect the other side.

The most striking feature about perinephric infection is the silence. The onset is insidious, and it may be days or weeks before local pain is experienced. This is usually felt in the loin and may become worse on deep breathing. The most important clinical findings are a tender fixed renal swelling with the usual general signs of infection, such as tachycardia, pyrexia or leukocytosis. Urinary symptoms do not appear,

20. Moore, T.: Juxtarenal Infections, Brit. J. Urol. **13**:1-7 (March) 1941.

and the urine is normal. Intravenous urography is sometimes useful in disclosing a deformity of the renal pelvis due to pressure of the abscess. Another important point is limitation of the normal respiratory excursions of the kidney. As diagnosis is likely to be delayed, patients are late in receiving correct treatment. The prognosis, however, is good, as drainage of the perinephric tissues alone suffices in most cases.

Secondary perinephric infections are those which arise from renal disease. The commonest are calculous disease (present in 7 of 10 cases in this series); others are noncalculous pyonephrosis, ascending pyelonephritis and renal carbuncle. Six patients were men, and 4 were women. The right side was affected in 4 cases, the left in 6. Treatment consists of correction of the underlying renal disorder, either before or after drainage of the abscess; thus the prognosis is poorer.

Paranephric infection is rarely primary and was present in only 1 case in this series. It is distinguished from perinephric infections by the fact that it lies outside the fascia of Gerota. The secondary infection reaches the paranephrium from contiguous structures, usually the colon. Two of the author's 50 cases were in this class. One was attributable to perforation of the colon by a fishbone and the second to carcinoma of the colon. Both infections proved fatal. In addition to signs of the underlying disease, there was evidence in these cases of general infection, together with local manifestations of inflammation in the nature of tenderness, and later, a mass. The exact situation of the lesion can be demonstrated only by careful investigation, including pyelography and enemas of barium sulfate, and often only by surgical exploration. Owing to the nature of the underlying disease and of the organisms concerned, which are derived from the colon, it can be readily understood that recovery is uncommon.

Atcheson [21] states that perinephric abscess may present a variety of clinical pictures and that it should always be considered as a possibility in cases of prolonged fever. In most cases, a pyogenic lesion occurs in the renal parenchyma before the perirenal space is involved. Secondary involvement of the perinephric space may occur by direct rupture of the abscess or may follow the veins and the lymphatics between the kidney and the perinephric space.

Two main groups of lesions precede the renal lesion, namely, (1) distant foci of infection, such as furuncles, and (2) chronic diseases of the kidney itself, such as calculi or pyonephrosis. The abscesses occur most commonly among men between the ages of 25 and 45 years. The onset is usually prolonged, and the diagnosis is seldom made before the patient has had symptoms for five or six weeks. Roentgenograms are becoming more important in diagnosis, but too much emphasis should not be placed on negative roentgenograms.

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21. Atcheson, D. W.: Perinephric Abscess with a Review of One Hundred and Seventeen Cases, J. Urol. **46**:201-208 (Aug.) 1941.

Practically all patients have pain, costovertebral tenderness, fever and leukocytosis. In a great many cases, however, some of the commonly stressed findings, such as spasm of the psoas muscle, flexion of the hip and changes in the urine, are absent. The postoperative course is prolonged and coupled with a high mortality rate.

The only treatment is incision and drainage with postoperative supportive measures. It is best not to close the wound too tightly, and in certain types of cases, a counterincision in the wall of the lower portion of the abdomen will facilitate recovery.

Pyelonephritis.—Hyams and Kenyon [22] present the clinical and pyelographic features of the early, intermediate and terminal stages of what they term "localized obliterating pyelonephritis" and stress the possibility of the development of these signs in the course of pyelonephritis and calculus disease. They express the belief that many patients who have pyelonephritis are not examined completely. Manifestly normal urograms and negative cultures do not necessarily insure complete arrest of the inflammatory process. Satisfactory diagnostic data can be obtained only by means of complete ureteropyelograms with occlusion catheters, and in the presence of the slightest suggestive change these studies should be repeated at suitable intervals over a long period. In certain cases in which an early tendency toward obliteration is recognized, eventual scarring and contraction may develop despite chemotherapy and local instrumental treatment.

When advanced or terminal changes have supervened, partial nephrectomy should be considered in instances in which the process is definitely limited to a suitable portion of the kidney. It seems that the intensive treatment of pyelonephritis prior to the occurrence of peripelvic extension is the most logical prophylactic measure.

Hypertension.—Riggs and Satterthwaite [23] report an unusual anomaly, a single kidney and ureter on the right side with obstruction of the renal artery by a small dissecting aneurysm and a localized sclerotic plaque in a case of hypertension. The development of hypertension in the acute phase in this case may have been initiated by partial occlusion of the lumen and the three branches of the main renal artery by the aneurysm. Riggs and Satterthwaite state that hypertension, especially that which is sudden in onset, no matter what the age of the patient, appears to warrant complete investigation of the renal arteries for abnormalities.

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22. Hyams, J. A., and Kenyon, H. R.: Localized Obliterating Pyelonephritis, J. Urol. **46**:380-395 (Sept.) 1941.

23. Riggs, T. F., and Satterthwaite, R. W.: Unilateral Kidney with Partial Occlusion of the Renal Artery Associated with Hypertension: Case Report, J. Urol. **45**:513-518 (April) 1941.

(To Be Concluded)

News and Comment

American Association of Industrial Physicians and Surgeons and American Industrial Hygiene Association.—The American Association of Industrial Physicians and Surgeons and the American Industrial Hygiene Association will hold their joint annual convention in Cincinnati April 13 to 17, 1942. Medical and hygienic problems associated with the present huge task of American industry will be presented and discussed in clinics, lectures, symposiums and scientific exhibits. The meeting will provide a five day institute for the interchange and dissemination of information on new problems, as well as for the consideration of up-to-date methods of dealing with those that are well known. The industrial physicians have taken responsibility for the program of the first two and one-half days and the hygienists for that of the remaining two and one-half days, but most of the subjects chosen for discussion will be of interest not only to physicians but to industrial engineers and executives.